"TO CORRELATE THE RELATION BETWEEN INSULIN RESISTANCE AND SERUM TRIGLYCERIDE LEVEL IN EUGLYCEMIC CIRRHOTICS"

Dissertation submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

CHENNAI

In partial fulfilment of regulations

For award of the degree of

M.D (GENERAL MEDICINE)

BRANCH – 1

KILPAUK MEDICAL COLLEGE

CHENNAI 600 014

April 2016

BONAFIDE CERTIFICATE

This is to certify that dissertation named **" TO CORRELATE THE RELATION BETWEEN INSULIN RESISTANCE AND SERUM TRIGLYCERIDE IN EUGLYCEMIC CIRRHOTICS**" is a bonafide work performed by DR.KIRUTHIKA S, postgraduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in fulfilment of regulations of The Tamilnadu Dr.M.G.R Medical University for the award of M.D. Degree Branch I (General Medicine) during the academic period from 2013 to 2016.

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ACKNOWLEDGEMENT FROM THE GUIDE

This dissertation work done by Dr.KIRUTHIKA.S on the topic "**TO CORRELATE THE RELATION BETWEEN INSULIN RESISTANCE AND SERUM TRIGLYCERIDE LEVEL IN EUGLYCEMIC CIRRHOTICS"** was under my supervision for the entire duration of the study and I ensure that the candidate followed the rules of the ethical committee.

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DECLARATION

I solemnly declare that this dissertation **"TO CORRELATE THE RELATION BETWEEN INSULIN RESISTANCE AND SERUM TRIGLYCERIDE IN EUGLYCEMIC CIRRHOTICS"** was prepared by me at Government Royapettah hospital, Chennai, under the guidance and supervision of **Dr.S.MAYILVAHANAN.S.M.D.,** Professor,Department of Internal Medicine, Government Royapettah Hospital, Chennai. This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfilment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine)**.

Place: Chennai

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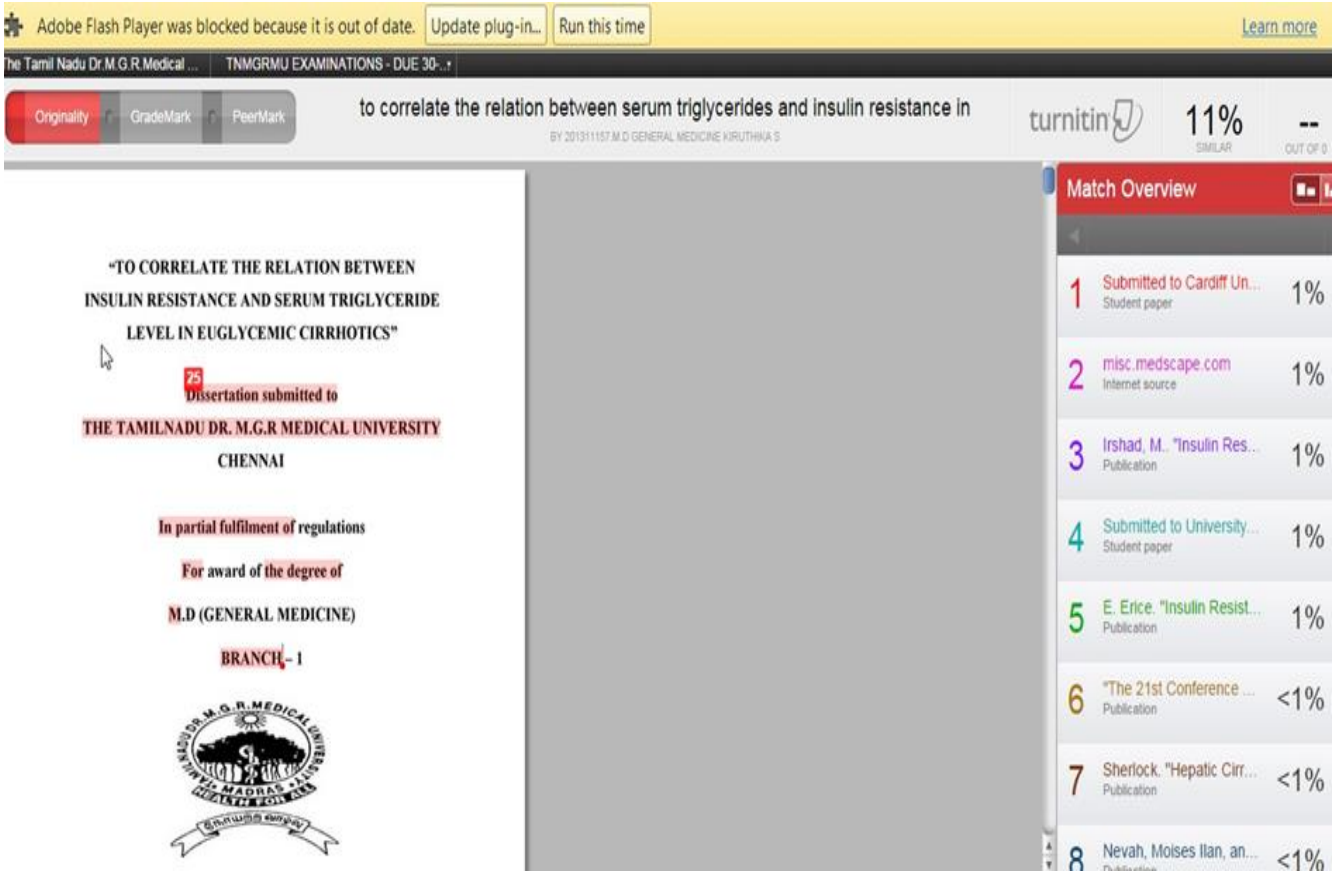
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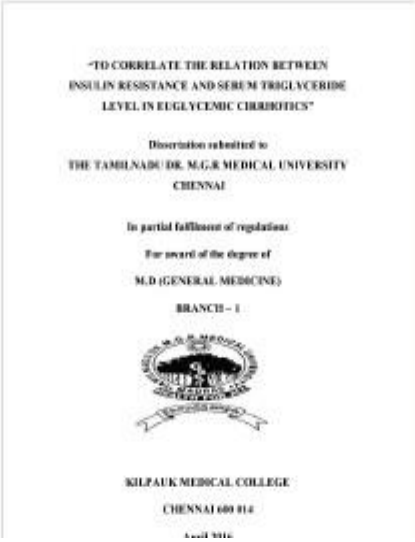

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ABBREVIATIONS

NAFLD: NON ALCOHOLIC FATTY LIVER DISEASE

HRS: HEPATORENAL SYNDROME

ANA: ANTI NUCLEAR ANTIBODY

LKMA: LIVER KIDNEY MUSCLE ANTIGEN

SLA: SOLUBLE LIVER ANTIGEN

SMA: SMOOTH MUSCLE ANTIBODY

HOMA : HOMEOSTATIC MODEL ASSESSMENT

IR : INSULIN RESISTANCE

IRS: INSULIN RECEPTOR SUBSTRATES

CRP: C REACTIVE PROTEIN

HCV: HEPATITIS C VIRUS

ADA: AMERICAN DIABETES ASSOCIATION

CTP: CHILD TURCOTT PUGH

HDL: HIGH DENSITY LIPOPROTEIN

LDL: LOW DENSITY LIPOPROTEIN

VLDL: VERY LOW DENSITY LIPOPROTEIN

NEJM: NEW ENGLAND JOURNAL OF MEDICINE

INTRODUCTION

INTRODUCTION

Liver is a major site for various metabolic, synthetic and excretory functions. Cirrhosis of liver causes dearrangements in all functional aspects of liver. Cirrhosis can be due to alcohol, viral infections like hepatitis B and C, metabolic causes like non alcoholic fatty liver disease, Wilson's disease, inherited diseases like hemochromatosis and autoimmune hepatitis .Bohan et al [(1)] described first about occurrence of diabetes in cirrhosis, which was later termed as hepatogenous diabetes by Megyesi et al [(2)]. It is found that 57 % of patients with cirrhosis develop insulin resistance. Diabetes can occur in 14 % of patients and impaired glucose tolerance in 60- 80% of cirrhotics[(3,4)].

Insulin resistance is described as normal or elevated insulin producing attenuated insulin response[(5)]. Insulin resistance in cirrhosis can be due to impaired clearance of insulin by liver due to hepatocellular fibrosis or porto systemic shunting of insulin or impaired feedback regulation of insulin or increased pancreatic insulin secretion but the exact mechanism is still unclear. Many studies concluded that insulin resistance could be due to insulin receptor and post receptor defects resulting in hyperinsulinemia [(6)]. Also in cirrhosis, portosystemic shunting causes decreased hepatic insulin and increased systemic circulating insulin.

Hyperinsulinemia thus occurred has multiple adverse effects on vascular bed. Patients with cirrhosis and insulin resistance need regular glycemic monitoring as they may develop impaired glucose tolerance and diabetes in future which has definite clinical implications in the form of decrease response to treatment, rapid progression to fibrosis, hepatocellular carcinoma risk and increased complications due to cirrhosis.

Lipid abnormalities have been reported in liver diseases. There are various results from different studies. This study is intended to find any relation between triglycerides and insulin resistance in euglycemic cirrhotics.

AIM & OBJECTIVES OF THE STUDY:

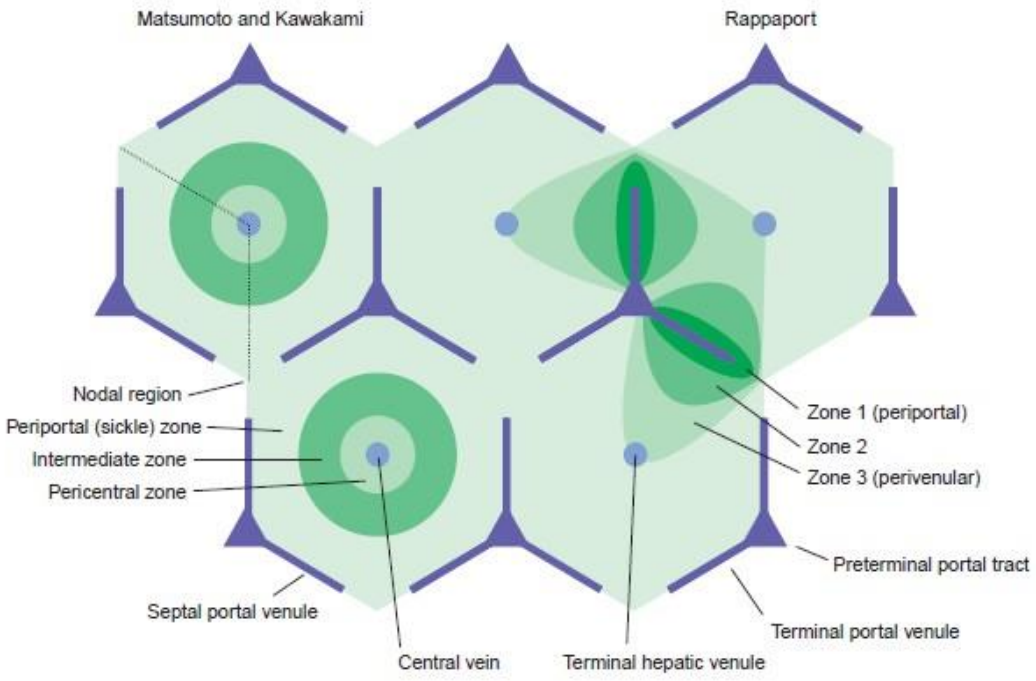
1. To establish that cirrhosis of liver is an insulin resistant state.
2. To establish the role of triglycerides in insulin resistance in patients with cirrhosis of liver

REVIEW OF LITERATURE

REVIEW OF LITERATURE

LIVER:

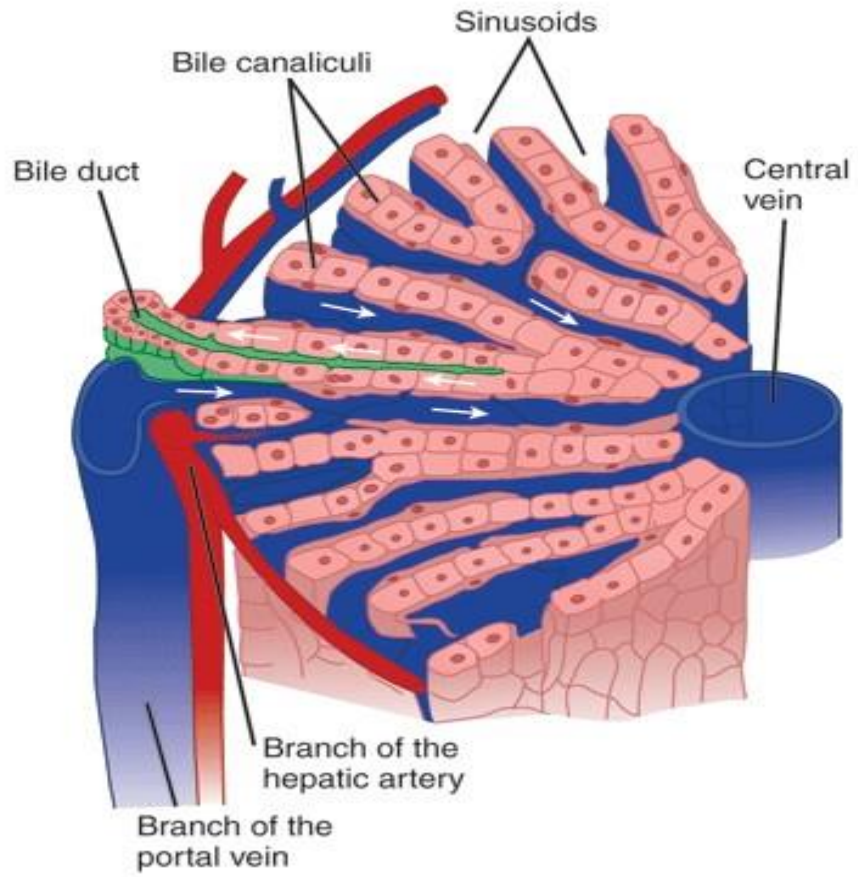
Liver is the largest gland in our body performing various secretory, excretory and metabolic functions. It weighs about 1400-1600 gram[(7)], constituting 2.5% of body weight. It extends from right fifth intercostal space along midclavicular line upto right costal margin. The size is about 12-15 cm in the coronal section and 15-20 cm in the transverse axis. The microarchitecture of liver can be discussed as lobular architecture and acinar model.



PICTURE 1: Microarchitecture of liver

BLOOD SUPPLY:

Liver receives 75% of its blood supply though portal vein and 25% from hepatic artery. The vessels enter liver via porta hepatis and they branch within the liver substance to form portal triad [10,11] which includes branches of hepatic artery, portal vein and bile duct.



PICTURE 2: Portal triad –portal vein, bile duct and hepatic artery

FUNCTIONS OF LIVER:

METABOLIC :

The liver is the final resort of all metabolic functions governing carbohydrate, protein and lipid metabolism in multiple ways.

- The key function in glucose metabolism is storage of glucose in the form of glycogen in well fed state and performing glycogenolysis and gluconeogenesis in fasting state. Glycogen stored in liver is the major source of energy for rapidly glucose requiring tissues like RBC, retina, renal medulla and brain. Glycogen stores in liver can supply glucose upto 2 days before gluconeogenesis occurs. Hence it is not uncommon to get hypoglycemia in chronic liver disease patients.
- Fatty acid undergoes beta oxidation forming acetyl coenzyme A which enters citric acid cycle and gives energy.
- Liver helps in protein metabolism in formation of urea from ammonia and deamination of amino acids.
- The synthesis of cholesterol, phospholipids and various lipoproteins and plasma proteins occur in liver.
- Apolipoproteins are proteins synthesised by liver. It combines with triglycerides,cholesterol, cholesterol esters to form lipoproteins. These lipoproteins mediate transport of lipids from liver to tissues and tissues to liver and other organs. Lipoproteins are classifieds according to their

relative density which is inversely proportional to the size. In the order of increasing density they are:

- Chylomicrons
- Very low density lipoproteins
- Intermediate lipoproteins
- Low density lipoproteins
- High density lipoproteins

CIRRHOSIS OF LIVER:

Cirrhosis is derived from *scirrhus a Greek word*, meaning orange or tawny. Cirrhosis, a final pathway for a wide variety of chronic liver disease, is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules [(12)].

The three important morphological features described pathologically includes:

- Bridging fibrous septa

Fibrous strands may occur between portal tracts and between portal tract and terminal hepatic vein. Following hepatocellular necrosis, healing occurs by deposition of collagen followed by remodelling .Fibrosis is the key feature of cirrhosis indicating progressive damage to the liver.

- **Parenchymal nodules:**

  Nodules are due to regeneration of hepatocytes surrounded by fibrosis.

- Architectural disruption of the entire liver is due to diffuse parenchymal injury and fibrosis.

  Pathologically it can be micronodular or macronodular depending on the size.

  Clinically it can be broadly classified as compensated cirrhosis or decompensated. The development of jaundice, hepatic encephalopathy, bleeding from varices, ascites and hepatocellular carcinoma indicates decompensation. Four clinical stages have been proposed. Stage 1 and 2 are compensated cirrhosis. Stage 3 and 4 are decompensated cirrhosis.

  Stage 1: Absence of varices and ascites

  Stage 2: Presence of varices without bleeding and absence of ascites

  Stage 3: Ascites with or without esophageal varices

  Stage 4: Variceal bleeding with or without ascites

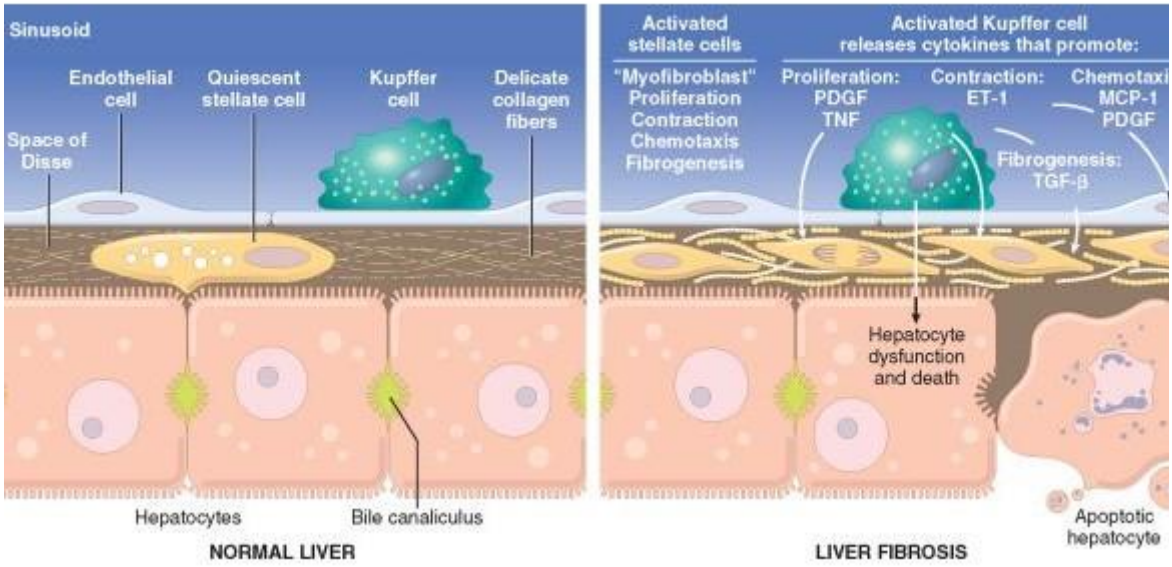
ETIOLOGY OF CIRRHOSIS

VIRAL	Hepatitis B virus Hepatitis C virus
TOXIC	Alcohol Arsenic
AUTOIMMUNE	Autoimmune hepatitis Primary biliary cirrhosis Primary sclerosing cholangitis
METABOLIC	Alpha 1 antitrypsin deficiency Hemochromatosis Glycogen storage diseases Wilson s disease Non alcoholic fatty liver disease Galactosemia
BILIARY	Atresia Stone Tumor
VASCULAR	Budd chiari syndrome Cardiac cirrhosis
GENETIC	Cystic fibrosis Liposomal acid lipase deficiency

PATHOGENESIS

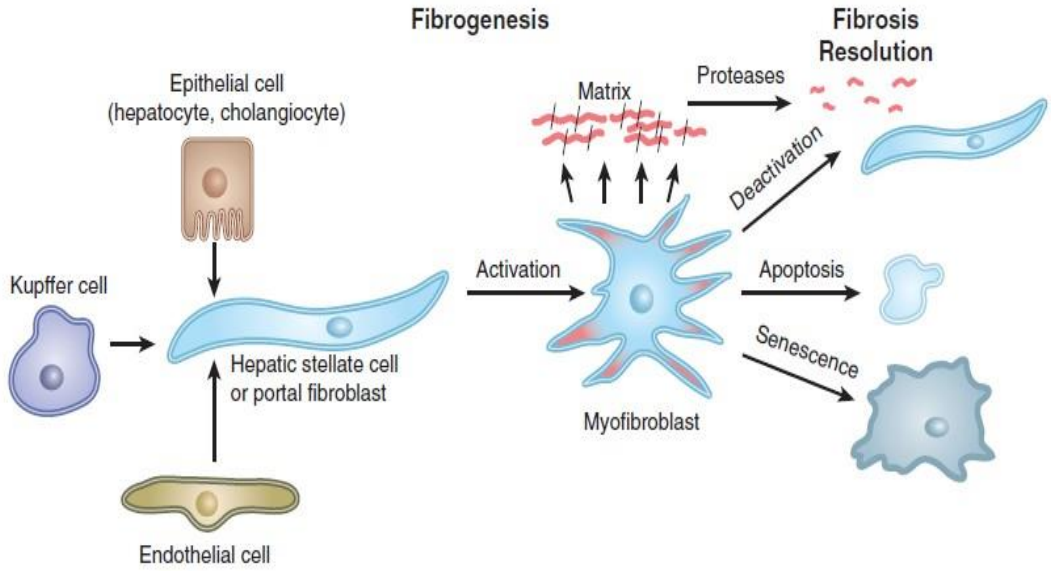
Fibrosis is the healing process to any injury in our body. Following an injury to liver, as a process of normal wound healing, there may be abnormal matrix deposition which differs both qualitatively and quantitatively[14]**:** This happens irrespective of the type of insult[15]. The key event in overall pathogenesis is sub endothelial collagen deposition in space of Disse leading to disruption of normal sinusoidal function[16].

Following liver injury, there are various alterations in the normal extracellular matrix leading to upregulation of many cellular receptors which mediate interaction between inflammatory cells and endothelium. Increase in expression of fibronectin in the cells is the earliest response which creates an environment for fibrosis. The hepatic stellate cells in the subendothelial space are also termed as Ito cells, perisinusoidal cells, fat storing cells are the main sources of extracellular matrix[17]. Under various cytokines from inflammatory cells, they assume phenotypic resemblance to myofibroblasts with contractile property. Stellate cell activation refers to "the transition from a quiescent vitamin A-rich cell to a highly fibrogenic cell characterized morphologically by the enlargement of rough endoplasmic reticulum, diminution of vitamin A droplets, ruffled nuclear membrane, appearance of contractile filaments, and proliferation".



PICTURE 3: liver fibrosis

Due to fibrosis, vascular channels are contracted and liver becomes small with severely compromised blood to hepatocytes. Finally interaction between hepatocytes and plasma in secreting various substances is severely impaired. Jaundice occurs due to disruption of portal tracts by fibrosis.



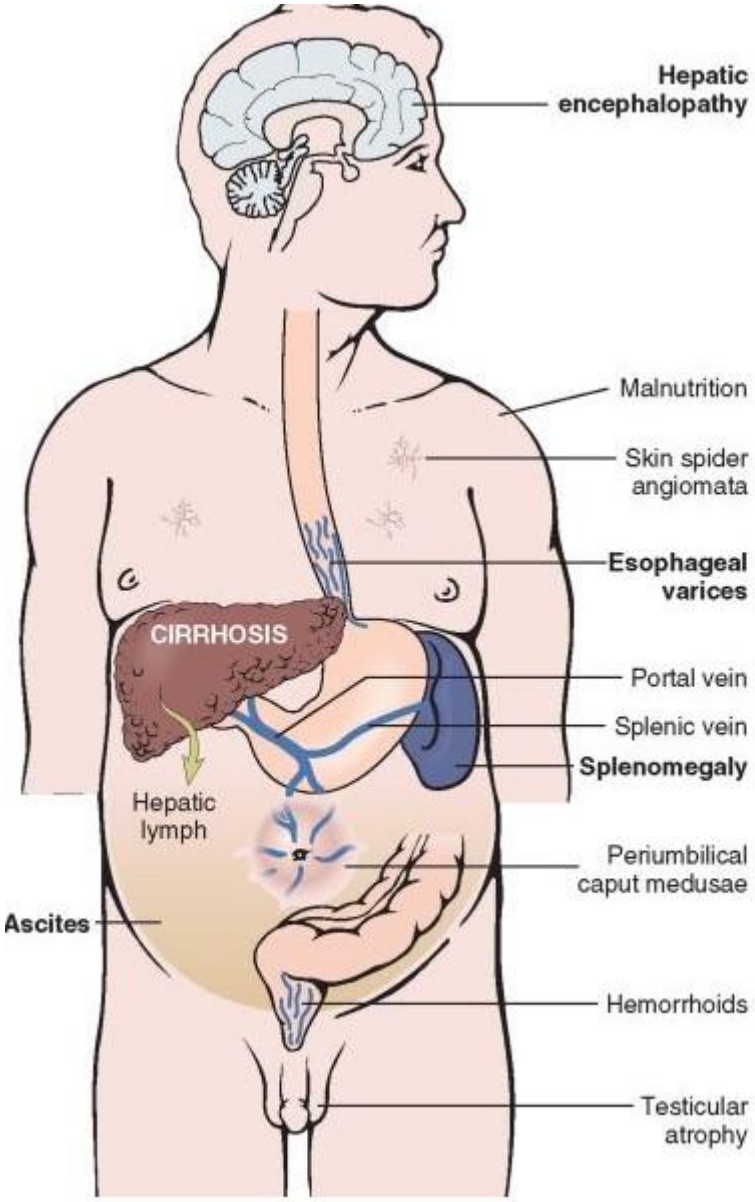
PICTURE 4:overview of pathogenesis and reversal of fibrosis

Reversal of fibrosis occurs due to myofibroblast deactivation, apoptosis or senescence. Matrix proteases can also achieve resolution of fibrosis.

PICTURE 5: Showing fibrosis in the portal tract by Mason Trichrome stain, expansion of portal tract, but surrounding acinar parenchyma is normal.

CLINICAL MANIFESTATIONS:

Although there are many causes of cirrhosis, the clinical features[18] that come to light are features of hepatocellular failure or complications of cirrhosis.



PICTURE 6: Clinical features of liver cell failure

ASCITES: It is due to portal hypertension

HEMATEMESIS/ MALENA: Due to bleeding from varices

ALTERED CONSCIOUS LEVEL: It occurs because of hepatic encephalopathy.

EASY FATIGUABILITY: It is due to wasting, anorexia and decreased metabolism.

JAUNDICE: Alteration in bilirubin metabolism causes jaundice.

ABDOMINAL PAIN: Abdominal pain along with increasing distension is due to spontaneous bacterial peritonitis.

FEVER AND INFECTION :

About a third of them have low grade continuous fever due to elevated cytokines in liver disease. Normally portal filters and hepatic system are bacteriologically sterile but when extensive collaterals occurs gut bacteria gain access to systemic circulation. Common infections include spontaneous bacterial peritonitis, pneumonia and urinary tract infection.

FETOR HEPATICUS:

It is a sweetish slightly faecal smell in the breath of patients with hepatocellular failure. It is presumed due to elevated mercaptans from impaired methionine demethylation.

VASCULAR SPIDERS:

Spider naevi or spider angiomata is a central feeding arteriole with surrounding radiating vessels..

LIVER PALMS:

There is warmth and redness in palms especially in hypothenar and thenar eminences and also in soles.

WHITE NAILS:

It is the opacity of nails occuring especially in thumb and index finger bilaterally.

Though the etiology for white nails and palmar erythema is not known clearly it can be due to elevated estrogens levels.

COAGULOPATHY:

Liver is the principal site of production of all clotting factors like vitamin K dependent clotting factors like 2,7,9,10 and factor 5, 12, 13 except Von Willebrand factor. Coagulopathy in liver diseases can be due to the following reasons:

- Decreased synthesis of clotting factors
- Vitamin K malabsorption / deficiency due to antibiotics, drugs and cholestasis
- Decreased production of inhibitors of clotting
- Hyperfibrinolysis

- Decreased clearance of activated clotting factors by liver
- Increased risk of DIC in the setting of sepsis
- Platelets number is decreased due to hypersplenism, intrinsic defect and reduced synthesis due to reduced availability of arachidonic acid for prostaglandin synthesis.

ENDOCRINE CHANGES:

There is impotence, loss of libido, gynecomastia and loss of secondary sexual characters in male leading to feminization particularly in alcoholics. In female, there is ovulatory failure, infertility and erratic menstruations. All are proposed to be due to increase in estrogen receptors and their sensitivity in cirrhotics.

PROGNOSTIC SCORES:

Poor prognosis in cirrhosis is indicated by prolonged prothrombin time, ascites, advanced age, gastrointestinal bleeding, high serum bilirubin and alkaline phosphatase. Liver transplantation mandatates accurate scores to assess prognosis so that surgery can be done at right time

CHILD TURCOTT PUGH SCORE(CTP) score:

It depends on jaundice, ascites, encephalopathy,serum albumin con- centration and nutrition.It gives a good short - term prognostic guide. Prothrombin time can be used rather than nutritional status called as Child – Pugh modification and individual features are scored by severity. The

total score classifies patients into grade A, B or C.

Measure	1	2	3
Total bilirubin (mg/dl)	<2	2-3	>3
Serum albumin(d/dl)	>3.5	2.8-3.5	<2.8
Prolongation of prothrombin time	<4	4-6	>6
Ascites	None	Mild	Moderate-severe
Hepatic encephalopathy	None	Grade 1-2 or suppressed by medication	Grade 3-4 Refractory

Scores 5-6 : child A

7-9 : child B

10-15 : child C

MELD score:

It is Model for End stage Liver Disease and it was originally developed in Mayo clinic.

MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival.

It is calculated according to the following formula:

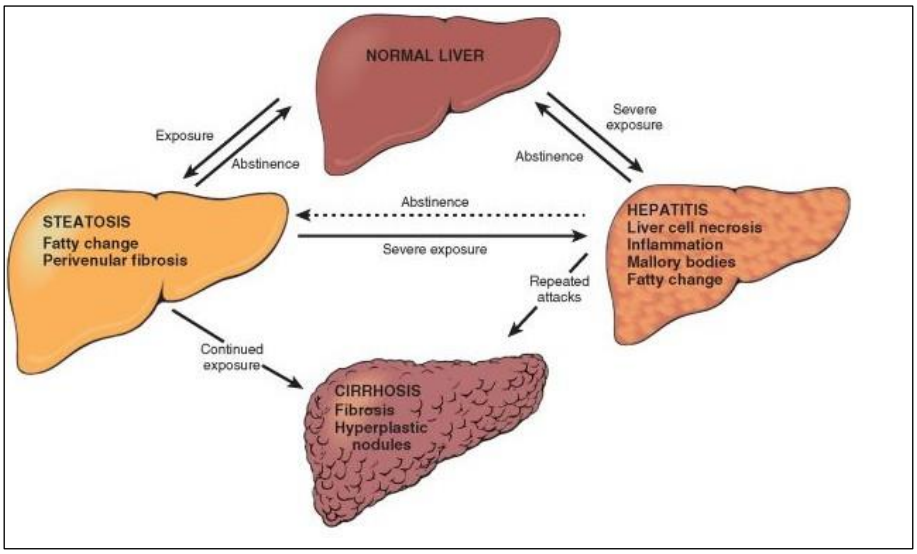
MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43× aetiology (0: cholestatic or alcoholic, 1: otherwise)

In interpreting the MELD Score in hospitalized patients, the 3 month mortality is:

- 40 or more — 71.3% mortality
- 30–39 — 52.6% mortality
- 20–29 — 19.6% mortality
- 10–19 — 6.0% mortality
- <9 — 1.9% mortality

ALCOHOLIC CIRRHOSIS

Alcohol, is the most important etiology for development of liver disease. The spectrum of disease ranges from mild fatty accumulation through steatohepatitis to frank cirrhosis. But not necessarily disease evolution occurs through stages, even multiple stages can be present in any patient. Fatty liver and steatohepatitis can be reverted if patient abstains from alcohol intake.



PICTURE 7: Stages of Alcoholic liver disease

RISK FACTORS [20-22]:

- Amount of alcohol: Alcohol consumption of about 60-80g/day in men and 20-40 g/day in women for 20 years
- Type of alcohol
- Sex : Women more sensitive due to higher body fat and reduced gastric alcohol dehydrogenase
- Presence of malnutrition

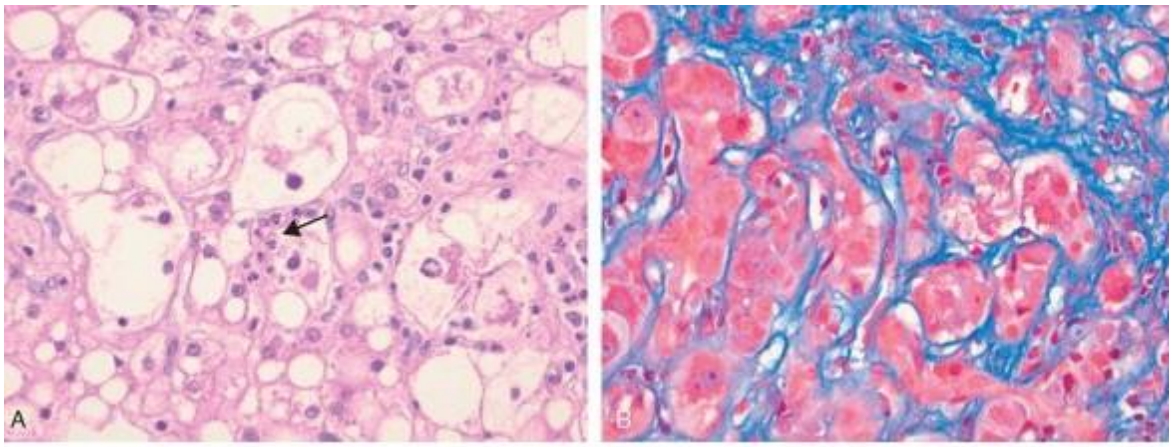
- Binge drinking
- Polymorphism of genes involved in metabolism of alcohol
- Coexistent hepatitis C virus infection and obesity

PATHOGENESIS:

Alcohol is metabolised by alcohol dehydrogenase, microsomal ethanol oxidising system(MEOS) CYP2E1 and little by peroxisomal catalase [23]. Acetaldehyde combines with proteins to form protein adducts which interfers with normal biological processes like microtubular formation, various enzyme activities and protein synthesis, trafficking and secretion. Due to hepatocyte injury by reactive oxygen species, kupffer cells get activated which may initiate fibrosis by programming stellate cells to fibroblasts through various proinflammatory mediators.

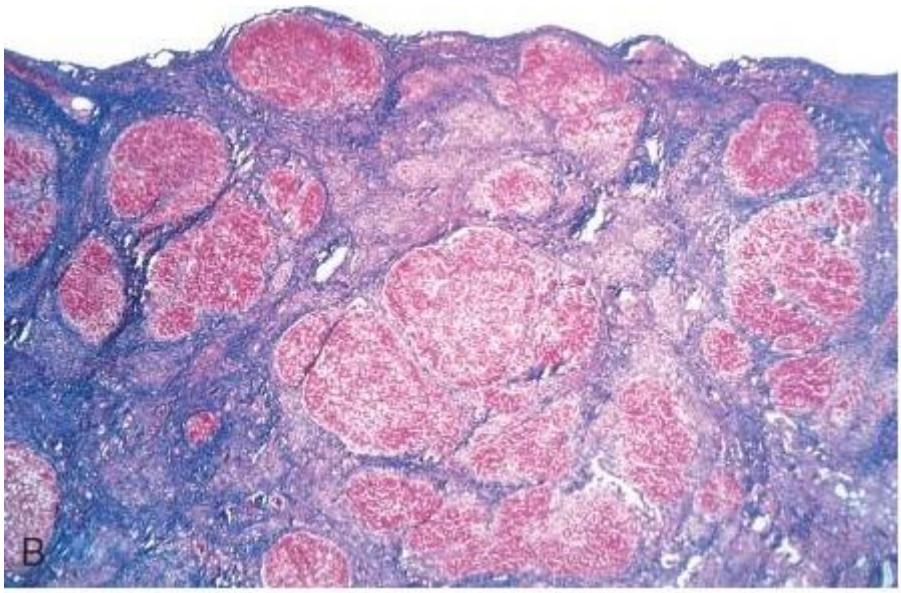
PATHOLOGY:

During initial stages, it is yellow tan, enlarged and fatty weighing more than 2 kilograms. Later it becomes small, shrunken, fibrotic and weight goes less than 1 kilogram. Cirrhosis initially is around the central vein termed as Lennaec cirrhosis. The fibrous septa is seen between portal tract-portal tract and from central vein to portal tract. At the end stage, it resembles like other causes of cirrhosis.



PICTURE 8 shows 1. Inflammatory cell infiltration 2. Mallory bodies (eosinophilic) surrounded by fibrosis.

PICTURE 9: Diffuse nodularity with green tinge due to bile stasis, hepatocellular carcinoma seen from the right lobe

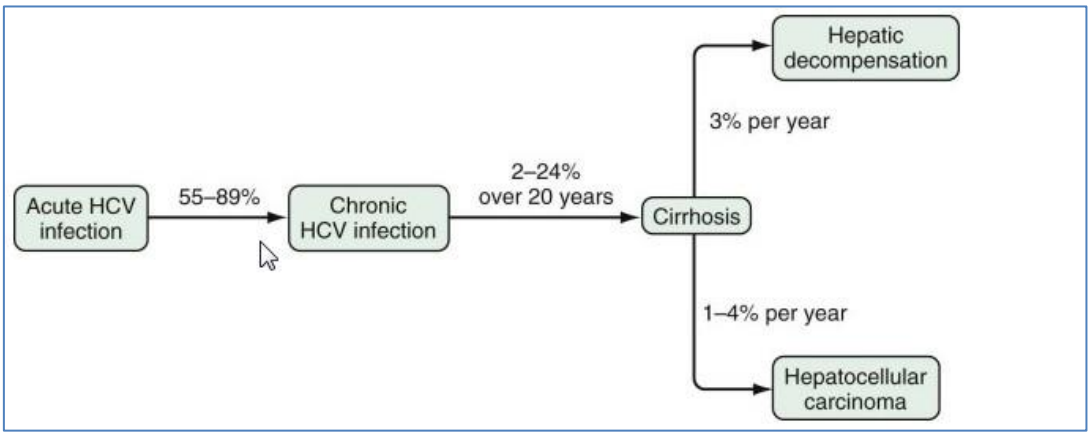


PICTURE 10: Microscopic picture shows nodules surrounded by fibrosis

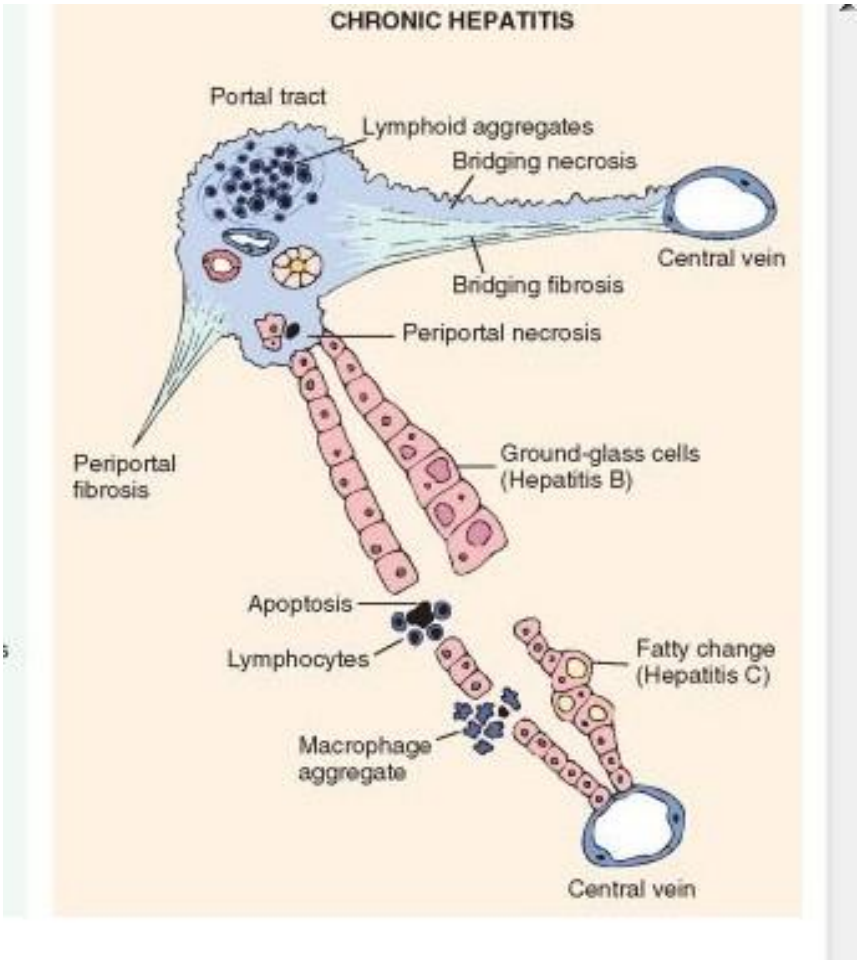
VIRAL HEPATITIS

Hepatitis B virus is a DNA virus belonging to hepadnaviridae family. Infection of HBV virus causes chronicity occurs in 2 %- 5% of cases. About one third of them develop cirrhosis and related complications. Hepatitis C virus is a single stranded RNA virus belonging to flaviviridae. About 3% of people are infected globally.

Hepatitis C virus is known for its chronicity and it progresses to cirrhosis over a period of 20 years. There are few other factors like alcoholic intake, coexistent hepatitis B infection, immunosuppression, insulin resistance, tobacco use and white race influence the disease progression to fibrosis.



PICTURE 11: Natural history of hepatitis C virus



PICTURE 12: Chronic hepatitis

NON ALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD)[26] indicates the presence of fatty infiltration of the liver and is defined as fat exceeding 5–10% of weight and frequently taken as >5–10% macrosteatotic hepatocytes in biopsy specimens.

In 1980, the disease was reported from Mayo clinic due to the resemblance with alcoholic cirrhosis. The disease is directly related to the obesity prevelance and severity in the population. It is considered as the hepatic manifestation of metabolic syndrome. The spectrum can be macrovesicular steatosis, hepatitis and finally cirrhosis. Patients are diagnosed many times due to incidental findings of elevated liver enzymes. Symptoms can be right upper quadrant pain and fatigue.

A detailed alcohol history is important before diagnosis. All other etiologies have to be ruled out. Finally liver biopsy gives picture like alcoholic cirrhosis. Management is weight loss and exercise.Anti oxidants like vitamin E and thiazolidienediones are approved for treatment. Multiple trials are ongoing to find newer treatment options in managing NAFLD.

WILSON'S DISEASE

Wilson's disease is an autosomal recessive disease due to ATP7B gene mutation in chromosome 13. It causes impaired biliary excretion of copper and hence hepatic accumulation leading to toxicity. It occurs in fourth to fifth decade[27,28]. It may present as hepatitis or cirrhosis with elevated transaminases with or without jaundice. Other features are dystonia, incoordination and tremors can occur due to deposition of copper in basal ganglia, psychiatric abnormality like crying, temper tantrums, arthritis, spontaneous abortions in female, Fanconi syndrome, nephrolithiasis and osteoarthritis. In eye, sunflower cataract and Kayser Fleischer rings can be seen.

Diagnosis can be done by 24 hour urinary copper and liver biopsy. Serum cerruloplasmin should not be used to make diagnosis as it is normal in 10% of patients. Treatment options are penicillamine, zinc, tetrathiomolybdate, trientine and liver transplantation. If there is severe decompensation, transplantation is the treatment. In pregnancy, presymptomatic, pediatric and for maintenance therapy, zinc is the treatment of choice.

HEREDITARY HEMOCHROMATOSIS

Initially though it was thought to be a haematological disease, later it was found to be a disorder of iron metabolism. In 1996, HFE gene mutations (C282y and H63D) in short arm of chromosome 6 was found to be the cause for hereditary hemochromatosis [29]. Secondary iron overload can present with same features. Symptoms can be myalgia, arthralgia, anorexia or features of chronic liver disease. Features due to iron overload in various organs like cardiomyopathy, arrhythmias, skin hyperpigmentation, diabetes, arthritis can be there.

When the disease is suspected based on clinical features, family history or anything, transferrin saturation or ferritin level should be seen. Genetic testing is mandatory to confirm diagnosis. Treatment is aimed at maintaining iron levels by maintenance phlebotomy and treating complications of cirrhosis.

ALPHA 1 ANTITYPSIN DEFICIENCY

Alpha 1 antitrypsin deficiency is another metabolic cause for cirrhosis. Though the exact mechanism is not known, it is postulated that structural aberration, misfolding and accumulation of proteins within endoplasmic reticulum can play a role. The disease has to be suspected in any cirrhosis with portal hypertension or hepatocellular carcinoma when all the infections are ruled out. Histologically liver biopsy shows characteristic periodic acid Schiff positive diastase resistant globules which are polymerized alpha 1 antitrypsin protein.

INDIAN CHILDHOOD CIRRHOSIS

A serious liver disease affecting infants and young children was first reported in a paediatric meet conducted in Kolkata. It was initially termed as infantile cirrhosis or infantile biliary cirrhosis. There are specific histopathological changes in the established stages of disease. It is found that liver contain excess stainable copper far in excess than Wilson’s disease.

CRYPTOGENIC CIRRHOSIS

The term cirrhosis of unknown etiology has started declining after discovery of hepatitis B virus in 1965, hepatitis D virus and hepatitis C virus in 1989. After establishing criteria to diagnose autoimmune hepatitis and Non Alcoholic fatty liver disease, incidence of cryptogenic cirrhosis had still declined. To make it short it is a vanishing type of cirrhosis.

INVESTIGATIONS

- Hemogram:

  Anemia can due to nutritional cause, variceal bleeding, direct suppressive effect of alcohol on bone marrow.

  Thrombocytopenia is due to hypersplenism and decreased thrombopoietin production from liver.

- RENAL PROFILE:

  Elevated renal parameters can be seen in hepatorenal syndrome, sepsis and prerenal acute kidney injury in the setting of diuretics and bleeding.

- CHEST X RAY: To rule out hepatic hydrothorax

- LIVER FUNCTION TESTS:

  Elevated bilirubin in the setting of cirrhosis signifies advanced disease. Ratio of AST/ALT > 2 is suggestive of alcoholic

hepatitis. ALT is more elevated in viral etiology. If alkaline phosphatase is elevated hepatocellular carcinoma has to be ruled out. Low alkaline phosphatase should prompt us evaluate for Wilson s disease

- SERUM ALBUMIN: In cirrhosis, the levels are low and it is correlated well with disease severity and survival of patients.
- COAGULATION PROFILE
- ULTRASOUND ABDOMEN: To see the liver echotexture, size, presence of free fluid, collaterals in portosystemic areas and screening for hepatocellular carcinoma.
- PORTAL VEIN DOPPLER: To look for the size of portal vein, dilation and flow which may be static or reversed.
- ASCITIC FLUID ANALYSIS:

  Elevated leucocytes with PMN> 250 cells/cu.mm confirms the diagnosis of spontaneous bacterial peritonitis.

  Serum ascitic albumin gradient (SAAG) of >1.1 is 97% specific for diagnosing ascites due to portal hypertension.

  In cirrhosis, ascitic fluid protein will be < 2.5mg/dl.
- VIRAL MARKERS: HBsAg and anti HCV to be done to rule out viral etiology.
- SLIT LAMP EXAMINATION : To rule out KF ring
- SERUM CERRULOPLASMIN AND 24 HOUR URINE COPPER

- AUTOIMMUNE WORK UP: ANA, LKM1 ,SMA, SLA
- PRIMARY BILIARY CIRRHOSIS: Anti mitochondrial antibody against pyruvate dehydrogenase complex
- GENETIC ANALYSIS: for hereditary hemochromatosis
- NON INVASIVE METHODS TO MEASURE FIBROSIS:

  FIBROSCAN- Transient Elastography

  FIBROMETER
- UPPER GI ENDOSCOPY: Screening upper GI endoscopy should be done for all patients to rule out esophageal varices, fundic varices and gastropathy.

COMPLICATIONS

PORTAL HYPERTENSION

It is defined as hepatic venous pressure gradient more than 5mmHg.There is selective intrahepatic vasoconstriction and splanchnic vasodilatation in cirrhosis which is behind all the clinical features. The increased portal pressure is due to altered vasoactive factors, mechanical factors like capillarization of sinusoids, narrowing of vessels due to fibrosis and nodules disrupting the architecture. The increased portal pressure is decompressed into systemic circulation at the sites of portosystemic anastomosis forming collaterals.

The classic features include ascites, varices and splenomegaly. Management of portal hypertension is aimed at decreasing splanchnic blood flow through vasopressin analogues and beta blockers. Endoscopic therapy is aimed at prevention of variceal bleeding, controlling acute bleeding episode and for rebleeding prevention.

ASCITES

In cirrhosis, there is elevated nitric oxide in splanchnic circulation which causes pooling of blood in splanchnic system and hence decreased effective circulatory volume. It is perceived by kidneys as hypovolemia leading to activation of renin angiotensin system causing salt

and water retention [34]. Patient with ascites experiencing sudden increase should alarm the physician in ruling out hepatocellular carcinoma. Patients should be treated with salt restriction, fluid restriction if there is associated hyponatremia and diuretics like aldosterone antagonists and loop diuretics in a fixed combination of 4:1.

SPONTANEOUS BACTERIAL PERITONITIS

Bacteria in gut may translocate and reach mesenteric lymph nodes and infect the ascitic fluid. When the opsonin activity is poor, it results in spontaneous bacterial peritonitis [35]. When the opsonin activity is moderate it cuases CNNA (culture negative non neutrocytic ascites) and when it is good it causes sterile non neutrocytic ascites. Management includes antibiotics like third generation cephalosporins / fluroquinolones along with albumin to prevent hepatorenal syndrome.

RENAL FAILURE IN CIRRHOSIS

Acute renal dysfunction occurs in about 15% -25% of patients who are hospitalized with cirrhosis. It occurs in about 30 % of patients with any infection, 25% in alcoholic hepatitis and in 10% who undergoes large volume paracentesis[36,37].

HEPATORENAL SYNDROME

HRS is classified into two types- type 1 and type 2. Type 1 is rapidly progressive renal failure of creatinine > 2.5 mg/dl in a period of less than 2 weeks. Type 2 HRS is slowly progressive characterized by creatinine < 2.5mg/dl[38].

DIAGNOSTIC CRITERIA: It is defined by International Ascites club as follows:

1. Cirrhosis with ascites
2. Serum creatinine more than or equal to 1.5 mg/dl
3. No or insufficient improvement in serum creatinine level 48 hours after diuretic withdrawal and adequate volume expansion with IV albumin
4. Absence of shock
5. No evidence of recent use of nephrotoxic agents
6. Absence of intrinsic renal disease

HRS can be prevented by avoiding injudicious volume depletion like large volume paracentesis, diuretics and lactulose therapy, prompt diagnosis of any infection and SBP prophylaxis. Treatment of HRS includes management of any infection, avoiding any nephrotoxic agents, vasopressors like terlipressin, midodrine and octreotide or nor epinephrine. The ultimate goal is preparing the patient for liver transplantation.

HEPATIC ENCEPHALOPATHY:

The term includes “wide array of transient and neurologic and psychiatric manifestations usually in patients with chronic liver disease and portal hypertension” [39].

In cirrhosis lot of vasoactive mediators lead to splanchnic vasodilatation, impaired hepatic function and alteration in blood brain barrier. There is impaired ammonia clearance by liver through urea cycle. Portosystemic shunting causes elevated serum ammonia. It finally leads to brain swelling, astrocyte swelling and altered neurotransmitters like increased GABA[40]. There are many scoring systems to grade hepatic encephalopathy of which most accepted one is West haven criteria.

An elevated level of serum ammonia in a patient with impaired consciousness and cirrhosis may suggest hepatic encephalopathy [41]. False positives include GI bleeding, drugs like valproic acid, alcohol and diuretics. Management is aimed at correcting the precipitating factors antibiotics and laxatives. The one and three year survival rate after hepatic encephalopathy are 42% and 23 % respectively without liver transplantation.

HEPATOPULMONARY AND PORTOPULMONARY HYPERTENSION

Cirrhosis with portal hypertension alters multiple vascular bed. Two defined diseases in pulmonary system includes hepatopulmonary and portopulmonary hypertension.

HEPATOPULMONARY HYPERTENSION

It is defined as "widened arterial alveolar oxygen gradient in room air in the presence or absence of hypoxemia". In cirrhosis the inflammatory mediators particularly NO and TNFα are increased in the pulmonary bed which cause vasodilation and angiogenesis leading to hypoxemia. It is found in 30% of patients with cirrhosis evaluated for liver transplantation. Clinical features platypnea, progressive dyspnea, cyanosis and clubbing. Diagnosis is made by contrast echocardiography using agitated saline. Long term oxygen lowers hypoxemia and pentoxifylline has been studied in multiple trials.

PORTOPULMONARY HYPERTENSION

It occurs due to vasoconstriction and remodelling of resistance vessels increasing pulmonary artery pressure. Though exact pathophysiology is not known, elevated endothelin levels are proposed. Management options include vasodilators like prostaglandins, endothelin

receptor antagonists like bosentan, ambrisentan and phosphodiesterase inhibitors like sildenafil.

HEPATOCELLULAR CARCINOMA

It is the most common primary malignancy of liver [43]. It occurs in liver with cirrhosis due to any cause like alcohol, hepatitis B and hepatitis C and less commonly with hereditary hemochromatosis, Wilson's disease, non-alcoholic fatty liver disease, alpha 1 antitrypsin deficiency and autoimmune hepatitis. 5year cumulative risk of getting HCC in the setting of cirrhosis due to above mentioned causes is 5-30% which is maximal with hepatitis C and decompensation.

Worldwide it is hepatitis B contributing to 50% of cases and almost all of childhood cases are due to hepatitis B due to the risk of perinatal transmission in developing countries. Though hepatitis B virus can lead to HCC without cirrhosis, about 90% of cases are related to cirrhosis only.

The estimated risk of HCC with hepatitis C virus is 15-20 times than with those who are not infected. The risk is maximum with advanced hepatic fibrosis and cirrhosis [44]. Symptoms produced are of little value like dyspepsia, loss of apetite and weight loss. In patients with cirrhosis it may occur with decompensation like worsening of hepatic encephalopathy and increasing ascites.

Screening is reasonable in Asian men >40 years, Asian women > 50 years, family history of hepatocellular carcinoma and high viral load. The screening test of choice would be an ultrasound. Nodules of size upto 1cm needs 3-6monthly screening with ultrasound. Nodules of size 1-2 cm should be evaluated further. Alpha fetoprotein >200 ng/ml is suggestive and >400ng/ ml is very likely for hepatocellular carcinoma.

The diagnostic modality of choice is dynamic CT scanning [45,46]. Various staging systems are available in which Barcelona clinic staging system (BCLC) is widely used. Treatment options include liver transplantation, transarterial chemoembolization (TACE), radiofrequency ablation and systemic therapy with PDGF inhibitor sorafenib. In a randomnized trial it had a survival advantage of 10.7 month survival compared to 7.9 month for placebo. The drug is approved by FDA to treat CTP A and unresectable hepatocellular carcinoma.

The best strategy to prevent this disease is avoiding high rish behaviours, vaccination for hepatitis B virus and treatment of chronic hepatitis B and C. Nowadays national vaccination schedules have significantly reduced the incidence of HCC. There is moderately strong evidence for using antivirals for both hepatitis B and hepatitis C virus may significantly reduce but does not eliminate the risk of hepatocellular carcinoma. According to NEJM, several non randomized and one

randomized controlled study patients with HCV infection but without cirrhosis who are treated with interferon based regimen showed reduced incidence of hepatocellular carcinoma.

INSULIN:

Insulin is a polypeptide anabolic hormone synthesised in rough endoplasmic reticulum of beta pancreatic cells. It exerts it physiological role in maintaining glucose homeostasis and cell mitosis. It is transported to golgi apparatus for package, then to plasma membrane where release occurs by exocytosis. It has two chains A chain and B chain linked by two disulphide bridges.

INSULIN RECEPTOR:

It is a tetramer with two alpha and beta subunits belonging to tyrosine kinase receptor family. It is also the receptor for insulin like growth factor and insulin receptor- related receptor (IRR).The gene for insulin receptor is located in chromosome 9[(47)]. The two α subunits are located outside the plasma membrane and β subunits span the membrane. The tyrosine kinase activity is intrinsic to β subunit which is inhibited by α subunit. Removal of α unit or binding of insulin to α sub unit may cause derepression and cause enhanced tyrosine kinase.The knowledge of insulin receptors are evolutionarily very ancient described in drosophilia and porifera.

Binding of insulin to insulin receptor activates it through phosphorylation and then various insulin receptor substrates (IRS). It has multiple signal pathways like phosphatidyl inositol 3 kinase /Akt kinase and protein kinase pathway [48].

Insulin receptor substrates are cytoplasmic proteins that send signals from insulin receptor to initiate variety of cellular response. IRS 1 and IRS 2 are ubiquitous in our body [49], involved in glucose metabolism and insulin mediated mitogenesis .Also reported that IRS 2 is more important in insulin glucose signalling and metabolism. AKt promotes glycogen synthesis and supresses gluconeogenesis. In striated muscle, the same receptor causes translocation of GLUT 4 to plasma membrane which facilitates uptake of glucose into cells. A negative feedback emanating from activation of AKt/ phosphoinositol pathway cause termination of IRS substrate action.

Constant supply of glucose to vital organs like brain, RBC s and liver can occur without insulin action but adipose tissue and skeletal muscle can utilise glucose only under the action of insulin through GLUT 4 receptors. After a meal, efflux of GLUT 4 receptors into the membrane occurs to allow influx of glucose into the cell. In well fed state, insulin promotes glycogen storage in liver and storage of fatty acids in the form of triglycerides through of activation of lipoprotein lipase.

INSULIN RESISTANCE

Insulin resistance is defined as “the inability of exogenous or endogenous insulin to increase glucose uptake and utilization to the level occurring in normal population”.

EPIDEMIOLOGY:

Insulin resistance is found in all the races with clustering of cases among whites. The increased risk of cardiovascular disease among insulin resistant individuals is higher among middle aged individuals though risk increases with age. Acanthosis nigricans, a common physical finding in insulin resistance, though found in all races is reportedly high among Hispanics and Blacks.

Action of insulin at the insulin receptors produce two major functions like one in glucose metabolism and other in cell mitosis. In diabetes, resistance is present to glucose metabolism but cell growth is preserved. Insulin resistance occurs in the ligand –receptor- response pathway which can be at the insulin receptor level or at insulin response substrates. Therefore compensatory hyperinsulinemia occurs to maintain the glucose level in blood. Some defects are being demonstrated with reduced substrates or phosphorylation by these residues. Insulin resistance is a significant phenomenon that causes impaired glucose tolerance and diabetes.

Insulin sensitivity and insulin release are reciprocally related. Thus, insulin resistance results in increased release of insulin to normal lipid and glucose homeostasis. Some mediators signal the pancreatic beta cells in response to insulin resistance but failure of those to adapt significantly may cause inappropriate insulin release, IGT and may be diabetes. Inflammation and cytokines play a role in insulin resistance in metabolic syndrome. It is supported by increased C- reactive protein suggesting chronic low grade inflammation. In many studies, they have found increased CRP levels may predict cardiovascular disease and diabetes in future.

CAUSES OF INSULIN RESISTANCE:

- Prereceptor causes of insulin resistance include abnormal insulin mutations and anti-insulin antibodies.
- Receptor causes include the following:

Decreased number of receptors - failure to activate tyrosine kinase

Reduced binding of insulin

Insulin receptor mutations

Insulin receptor–blocking antibodies

- Post receptor causes include defective signal transduction and mutations of GLUT4.

CONDITIONS ASSOCIATED:

- It is a well-established in conditions like obesity, hepatitis C virus, metabolic syndrome, accelerated atherosclerosis.
- Aging: due to reduced GLUT 4 receptors
- Increased production of insulin antagonists: Cushing syndrome, acromegaly, and stress states, such as trauma, surgery, diabetes ketoacidosis and severe infection.
- Medications: glucocorticoids, cyclosporine
- Sodium: High sodium intake has been associated with increased glucocorticoid production and insulin resistance.
- Anti HIV therapy: Nucleoside analogues are associated.
- Insulin therapy: Low titre immunoglobulins are present in patients who take insulin which may cause prereceptor insulin resistance.

Obesity is the most common cause of insulin resistance and it is is associated mainly with postreceptor abnormality and also with a decreased number of insulin receptors.

INSULIN RESISTANCE IN CIRRHOSIS:

Bohan et al [(1)] described association between liver cirrhosis and diabetes, whereas Megyesi et al [(2)] termed it as hepatogenous diabetes where 57% of patients with cirrhosis are found to have insulin resistance. Hepatitis C virus, Non Alcoholic fatty liver disease and autoimmune hepatitis are found to be well associated with insulin resistance.

In AIIMS, Jain et al assessed glucose tolerance in euglycemic cirrhotics using insulin suppression test (Modified Hirano s method)[(51)]. They found that cirrhotics had higher 90 min and 120 min plasma glucose and 120 min serum insulin suggesting higher postprandial glucose and insulin. They have higher than normal insulin to produce normal glucose homeostasis. They concluded that cirrhotics have decreased insulin sensitivity or endogenous insulin resistance that precedes impaired glucose tolerance and diabetes.

A study was conducted in Italy by Nielson et al to find the pathogenesis of glucose intolerance in liver cirrhosis. They found that endogenous glucose release suppression was unaltered but there was a defect in uptake of glucose[(52)]. There was a defect in glucose utilisation even during physiological conditions. They concluded that carbohydrate intolerance in cirrhosis is due to insulin resistance which can be ascribed to

defective glucose uptake rather than abnormalities in glucose production and beta cell function.

Reasons for insulin resistance in cirrhosis are proposed to be:

- Insulin receptor/ post receptor defects
- Increased pancreatic insulin secretion due to pancreatic beta cell hypertrophy
- Elevated of insulin antagonists like cytokines, free fatty acids, glucagon, growth hormone and catecholamines
- Downregulation of insulin receptors
- Impaired removal of insulin by liver due to porto systemic shunting.

INSULIN RESISTANCE AND HEPATITIS C VIRUS [49]

Association of insulin resistance and HCV virus related cirrhosis was demonstrate by Allison et al., They found that HCV related cirrhosis developed diabetes more frequently than those of non HCV virus. Few cases have occurred even without cirrhosis[49]. Diabetes is associated with genotypes 1b, 2a and 4 and others may not develop insulin resistance. Similar insulin resistance was not present in hepatitis B implying hepatitis C virus has some role in causing diabetes.

The mechanisms proposed for insulin resistance in HCV virus are:

- **STEATOSIS:**

It is the accumulation of fat in hepatocytes. It is a major factor contributing to insulin resistance during liver diseases. It is described in 40-80% of patients with HCV related cirrhosis. Studies on mechanism of steatosis by HCV suggest that core protein inhibits microsomal triglyceride transfer protein activity and very low density lipoprotein secretion. It also impairs the expression of Peroxisome Proliferator-Activated Receptor.

- **Oxidative stress:**

It was noticed that HCV-core protein present within the outer membrane of mitochondria induces oxidation of mitochondrial glutathione and there is increased reactive oxygen species (ROS) production by mitochondrial electron transport complex I and III.

Insulin resistance is maximally related to genotype C. It is found to be associated with reduced response rate to ribavirin and interferons and rapid progression to fibrosis. Thus insulin resistance has important implications in disease progression and treatment options.

Pancreatic islet cell hypertrophy has been reported in biopsy of patients with liver cirrhosis. It is due to compensatory increase in beta cells to insulin resistance [(52)]. Takei et al proposed that islets in cirrhosis show higher proliferation and lower apoptosis to those without disease. Insulin resistance associated with cirrhosis was significantly associated with

development of portal hypertension in initial stages but later after portal hypertension develops [53], HOMA 2 index rises due to porto collateral circulation.

Insulin is proposed to stimulate endothelial NO production through phosphatidylinositol 3 kinase and serine threonine kinase signalling pathway [52]. As a consequence of insulin resistance, reduced signalling and increased NO production results in endothelial dysfunction and therefore can lead to multiple cardiovascular events.

The major causes of death in patients with insulin resistance and cirrhosis are complications of liver disease like chronic liver failure, gastrointestinal haemorrhage and hepatocellular carcinoma [53]. Therefore the major aim in managing patients with hepatogenous diabetes include reducing complications of cirrhosis and the incidence of hepatocellular carcinoma.

ASSESSMENT OF INSULIN RESISTANCE:

EUGLYCEMIC CLAMP [54]:

It is the gold standard for diagnosing insulin resistance as it considers the dynamic change in glucose levels. The goal is to acutely raise the blood glucose to a fixed state of about 125 mg/dl from the base value. The priming dose is given for 15 minutes and then maintenance dose for every five minutes till the study is finished. Therefore a constant glucose level has to be maintained by adjusting the rate of infusion.

In this situation, insulin is infused constantly to maintain levels above 100mu/ml. So glucose infusion equals glucose uptake into tissues producing euglycemic state. This represents the body's response to exogenous insulin.

Advantages:

- Helps to assess beta cell sensitivity and amount of glucose metabolised in response to hyperglycemic stimulus
- Assessment of early pulsatile and late maintenance insulin release
- Amount of glucose metabolised can be assessed
- After insulin administration, due to continuous infusion of glucose role of counter regulatory hormones are prevented and we may know the true insulin sensitivity of the tissues
- If labelled glucose is used, it may clearly give additional information

about site of clearance of insulin- liver vs periphery

Disadvantages:

- Time consuming
- Expensive
- Needs good laboratory setup
- Can’t be easily repeated

HOMA evaluation:

The Homeostatic model assessment is a validated tool to measure insulin resistance using fasting insulin and triglycerides. The first and original model was proposed by Mattew et al in 1985 and it is been on constant use for epidemiological purpose also. Recently with few changes in physiological parameters it is upgraded to a computer version HOMA 2[(55-57)]

.

HOMA1- 1R is calculated by the following formula:

HOMA1 -1R= fasting insulin (ц U/dl) * fasting glucose (mmol/L).

HOMA 2-IR is obtained through programmed HOMA calculator downloaded from The Oxford University for Diabetes, Endocrinology and Metabolism. Several studies suggest that HOMA 2 can be a useful tool to identify subjects with insulin resistance who are at risk of developing cardiovascular disease.

Though defining cut off values for defining insulin resistance using HOMA scale is under various study, we have taken a study conducted by Bruno et al as the reference which gives 2.7 for HOMA 1R and 1.8 for HOMA2 IR for defining insulin resistance.

TyG index[58]:

It is calculated using fasting glucose and fasting triglycerides. The formula is {ln (fasting triglycerides mg/dl)* fasting glucose mg/dl /2}. The cut off value is 4.6.

It is considered to be a mirror of gold standard euglycemic clamp in assessing insulin resistance and it has comparatively good sensitivity to HOMA 1 model though not superior to it. It can be effectively used epidemiologically for assessing insulin resistance when fasting insulin values are not available. But the major limitation it does not reflect the physiological changes of glucose and insulin. Although there is no clear correlation between insulin resistance and hypertriglyceridemia, it is proposed that elevated triglycerides in muscle impairs insulin sensitivity by altering muscle glucose metabolism.

QUICKI index: QUANTITATIVE INSULIN SENSITIVITY INDEX.

It is a surrogate marker for HOMA scale to define insulin resistance which showed comparable results with HOMA.

$$\text{QUICKI} = 1/\{\log(I^{\circ}) + \log(G^{\circ})\}$$

where I^0 is fasting insulin in mu/ml and G^0 is fasting insulin in mg/dl. Since it is the reciprocal of log transformed product of insulin and glucose, it is a dimensionless number. It reflects only hepatic insulin sensitivity.

LIPID PROFILE IN CIRRHOSIS

. Liver plays an important role in lipids and lipoprotein metabolism. Endogenous cholesterol synthesis from hepatic microsomes cause decrease in serum levels. Also HDL, LDL and apolipoprotein levels are reduced in cirrhosis. There were many studies previously conducted in various parts of world found that dyslipidemia is common in liver diseases like reduced cholesterol, HDL, LDL and TGL and suggested that cirrhosis is a state of hypolipidemia[59,60]. Also in cirrhosis energy is derived mostly by lipolysis because energy utilisation from glucose through glucose oxidation is impaired. Furthermore, their adipose tissue and lipid metabolism are insensitive to insulin. Thus, it is a state of hypermetabolism because energy expenditures are high due to increased utilisation of lipid stores.

Kackar et al. found that the serum cholesterol levels decreases progressively with the progress of alcoholic cirrhosis But there was an Indian study conducted in a north eastern teaching hospital showed elevated triglycerides and reduced LDL and total cholesterol occur in them. Previously it was found that serum triglycerides was higher in child class A than in child class B and C which is due to preserved ability for class A to synthesise VLDL than class B and C.

TRIGLYCERIDES AND INSULIN RESISTANCE:

Skeletal muscle constitutes about 40 % of body mass and 80% of glucose usage. Hence increased blood glucose in obesity and diabetes is associated with insulin resistance in skeletal muscle. Lipids are found to be the source of energy since the end of 1950. There is a critical link between muscle triglycerides and insulin sensitivity. Increased muscle triglycerides observed in obese and diabetes are linked with decreased insulin sensitivity. Hence excess lipid and lipid metabolites accumulation in the muscle are significantly associated with insulin resistance.

In this study, we have tried to find any relation of triglycerides with insulin resistance in cirrhosis.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was conducted in Government Royapettah hospital for a duration of 1 year from July 2014 to July 2015. The study was conducted after getting informed consent from all the patients involved in this study. Ethical committee clearance was obtained from Kilpauk Medical College.

STUDY DESIGN: It was designed as cross sectional study

STUDY POPULATION: 50

INCLUSION CRITERIA:

Patients with cirrhosis already proven by imaging who attends Medicine and Medical Gastroenterology outpatient clinic and inpatients in medical wards.

EXCLUSION CRITERIA:

1. Diabetes mellitus as defined by ADA with fasting blood glucose >126 mg/dl
2. Hepatitis C virus infection
3. Pregnancy
4. Lactation
5. Cardiac failure
6. Renal failure

7. Respiratory failure
8. Hepatocellular carcinoma
9. Presence of infection and acute decompensation in the prior 2 wk;
10. Prescription of hypolipidemic drugs , antihypertensives, corticosteroid, bronchodilator , vasoactive, or hypoglycemic agents within 1 month.

METHODOLOGY:

Patients who were already diagnosed to have cirrhosis and attending medical or medical gastroenterology outpatient clinics and inpatients in medical ward were taken into study. The sample size was set to be 50. A detailed clinical examination was performed. Height and weight were measured. Presence of ascites and pedal edema were noted. After getting consent from the patients following investigations were done:

1.Fasting insulin

2.Fasting blood glucose

3.Fasting serum triglyceride

4. Blood urea, Serum creatinine.

6.Liver function tests- bilirubin, AST,ALT, ALP, serum total protein, serum albumin

7. Prothrombin Time/ International Normalised Ratio (INR)

8.Ultrasound abdomen

BODY MASS INDEX:

Body mass index was calculated using the formula weight (kg)/ height* height(m). If ascites was present, then correction of 4 was given for weight.

INSULIN RESISTANCE:

HOMA 1R:

{fasting insulin (ц U/dl) * fasting glucose (mmol/L)}/22.5.

A value >2.7 is taken as insulin resistance.

HOMA2R:

Programmed calculator downloaded from university of oxford. http://www.dtu.ox.ac.uk/. Value of >1.8 is taken as insulin resistance.

TyG INDEX:

The formula is { ln (fasting triglycerides mg/dl)* fasting glucose (mg/dl) /2} . The cut off value is 4.6.

TRIGLYCERIDE LEVELS:

Fasting triglycerides were seen after 8 hours of overnight fasting.

Normal**:** Less than 150 mg/Dl

Borderline High**:** 150 - 199 mg/dL

High**:** 200 - 499 mg/dl

Very High**:** 500 mg/dL or above

RESULTS AND STATISTICAL ANALYSIS

The data obtained was analysed using SSPS software. Chi square test was used for comparison of dichotomous variables. A p value of <0.05 was taken as statistically significant value. Pearson correlation coefficient was used to compare the regression coefficient between two groups.

RESULTS

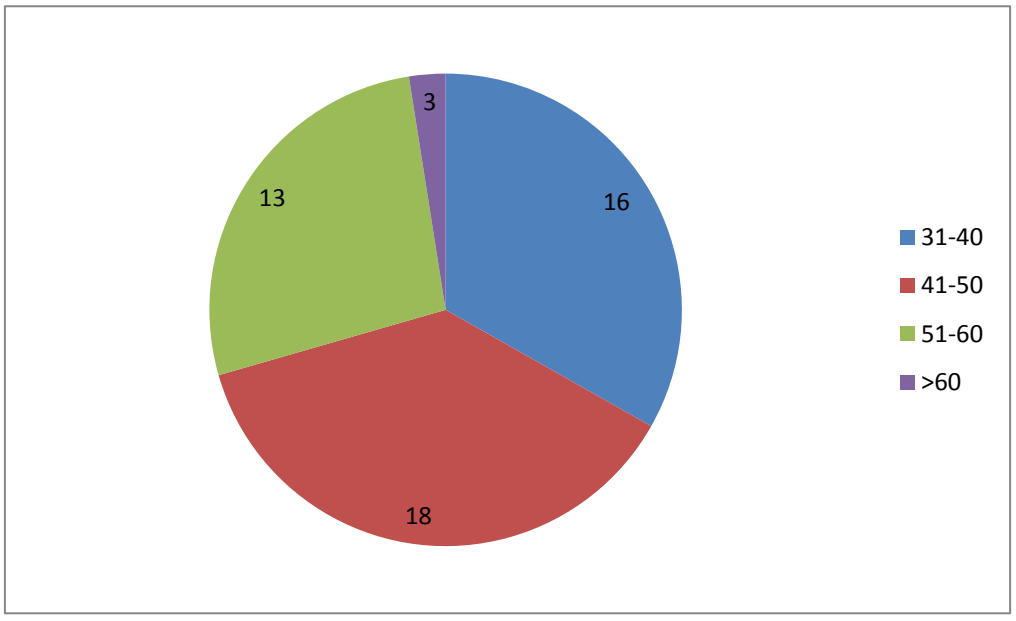
RESULTS

AGE DISTRIBUTION:

S no	Age	Frequency	Percent %
1	30-40	16	32
2	41-50	18	36
3	51-60	13	26
4	>60	3	6

This table shows age distribution of our study population.

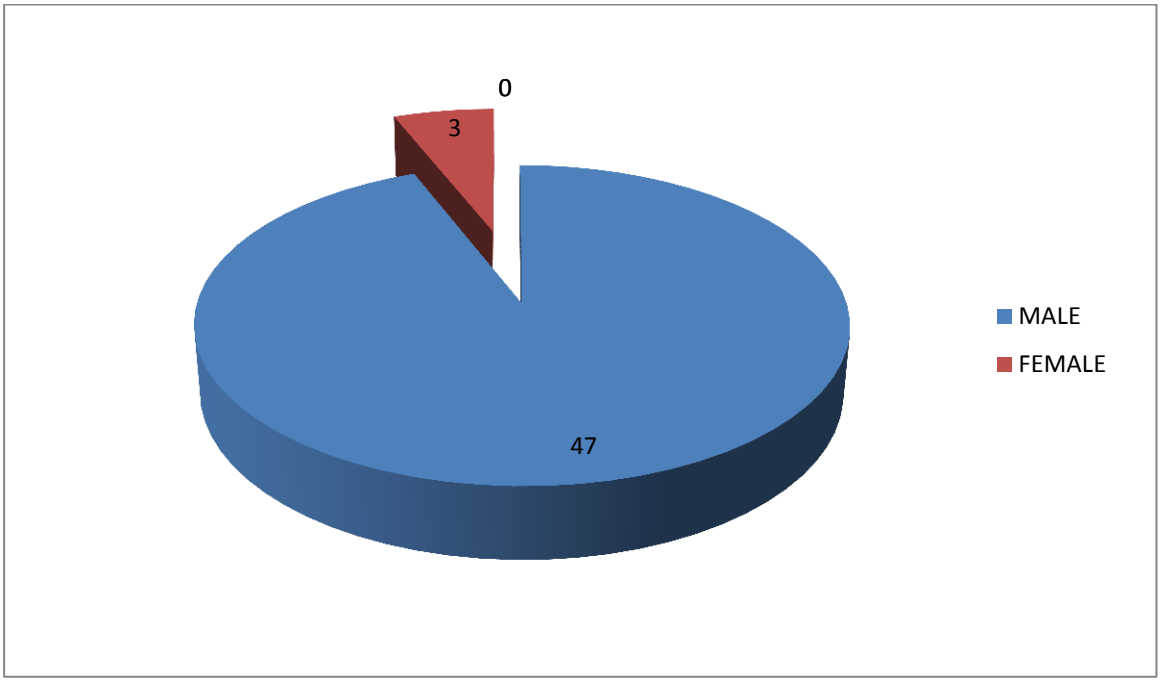
AGE IN YEARS:



Pie chart representing age distribution of patients in numbers

In this study about 18 patients in the age group 41-50 years are major contributors. All the patients are more than 30 years and maximum age in our study is 75 and minimum is 31.The mean age of study population is 46.18 ± 9.78 years.

SEX DISTRIBUTION:



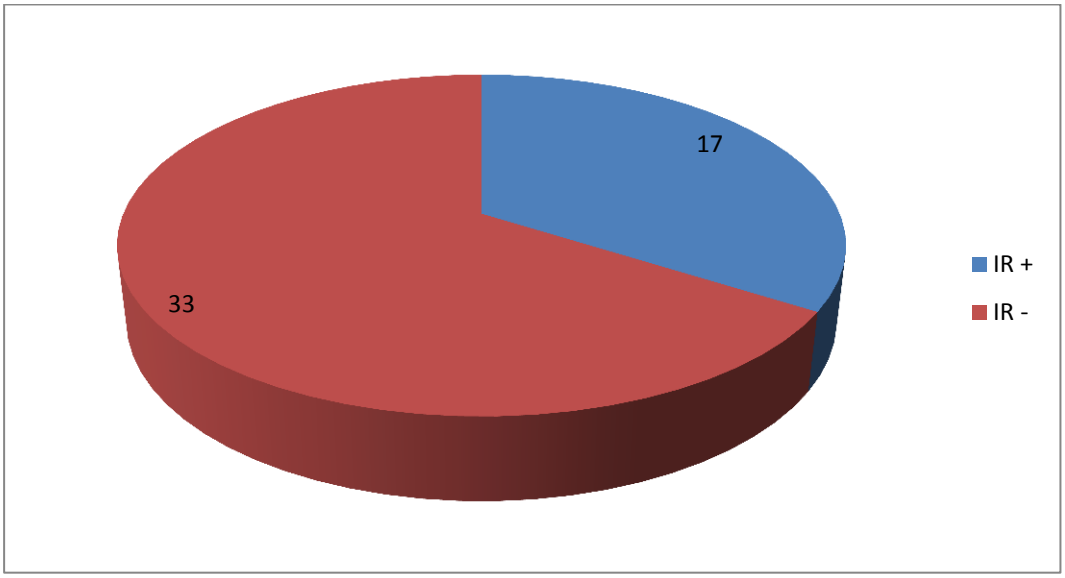
Pie chart showing sex distribution in our study in numbers.

Out of fifty cases, 47 cases are male and only 3 are female.

HOMA 1R:

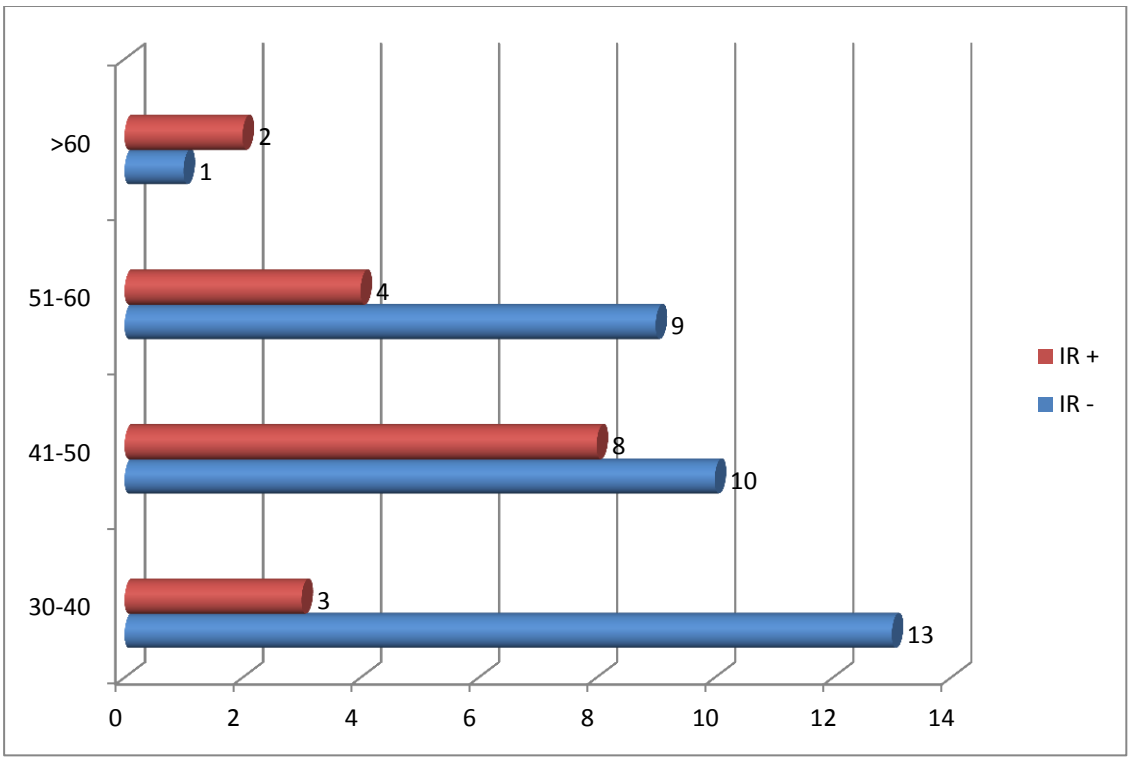
	Frequency	Percent	Valid Percent	Cumulative Percent	P value
IR -	33	66.0	66.0	66.0	0.024
IR +	17	34.0	34.0	100.0	
Total	50	100.0	100.0		

This table shows number and percentage of our study group showing insulin resistance according to HOMA1 IR and statistical significance



Pie chart showing distribution of insulin resistance as per HOMA 1R score. Number of patients are shown.

In our study, 17 patients out of 50 had insulin resistance by HOMA 1 which accounts for 34 % of patients which is statistically significant with p value < 0.001.



Bar diagram showing age wise distribution of IR by HOMA 1.

AGE VS HOMA 1R

Age in years		HOMA 1R		
		NO IR	IR +	Total
30-40	Count	13	3	16
	% within HOMA 1R	39.4%	17.6%	32.0%
41-50	Count	10	8	18
	% within HOMA 1R	30.3%	47.1%	36.0%
51-60	Count	9	4	13
	% within HOMA 1R	27.3%	23.5%	26.0%
Above 60	Count	1	2	3
	% within HOMA 1R	3.0%	11.8%	6.0%
Total	Count	33	17	50
	% within Age in years	66.0%	34.0%	100.0%
	% within HOMA 1R	100.0%	100.0%	100.0%

In this table, age wise distribution of presence and absence of insulin resistance is shown according to HOMA1 IR.

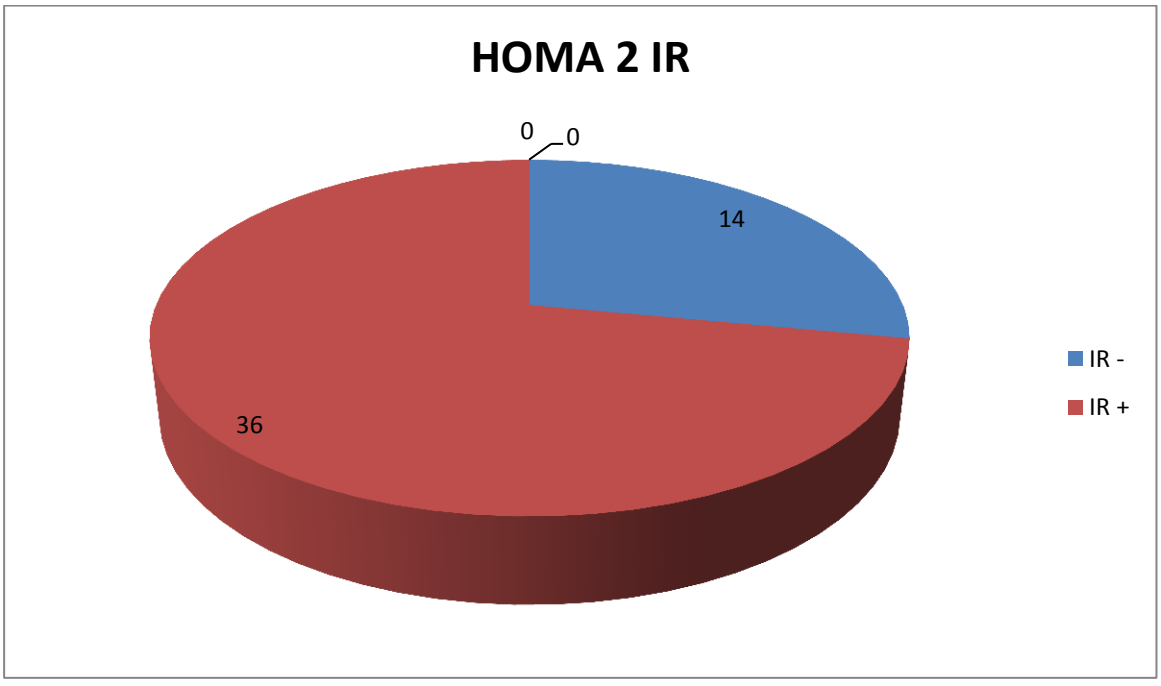
According to HOMA 1- IR calculated , in our study 17 patients had insulin resistance which comes to about 34%. Out of 17 patients who had insulin resistance, 3 patients (17.6%) were in the age group of 30-40 years, 8 patients

(47.1%) were in 41-50 years, 4patients (23.5%) were in 51-60 years and 2 patients (11.8%) were in more than 60 years age group.

HOMA 2:

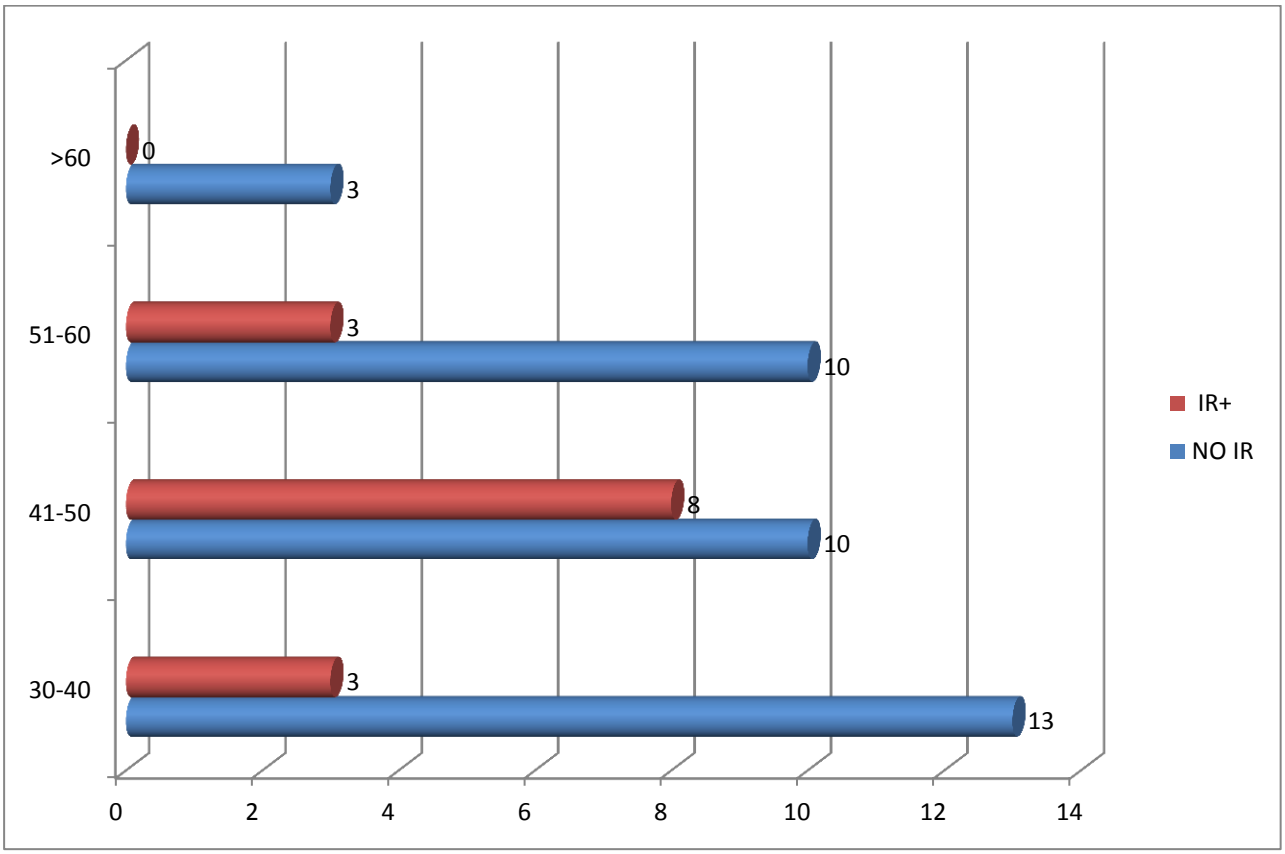
	Frequency	Percent	Valid Percent	Cumulative Percent	P value
IR -	36	72.0	72.0	72.0	0.002
IR +	14	28.0	28.0	100.0	
Total	50	100.0	100.0		

This table shows number and percentage of our study group showing insulin resistance according to HOMA2 IR score.



In this pie chart, number of patients showing insulin resistance according to HOMA 2 is shown.

In this study, out of 50 patients 14 patients (28%) had insulin resistance according to HOMA 2 IR score. It was statistically significant with p value of 0.002 (< 0.05).



Bar diagram showing age distribution of IR by HOMA2 IR

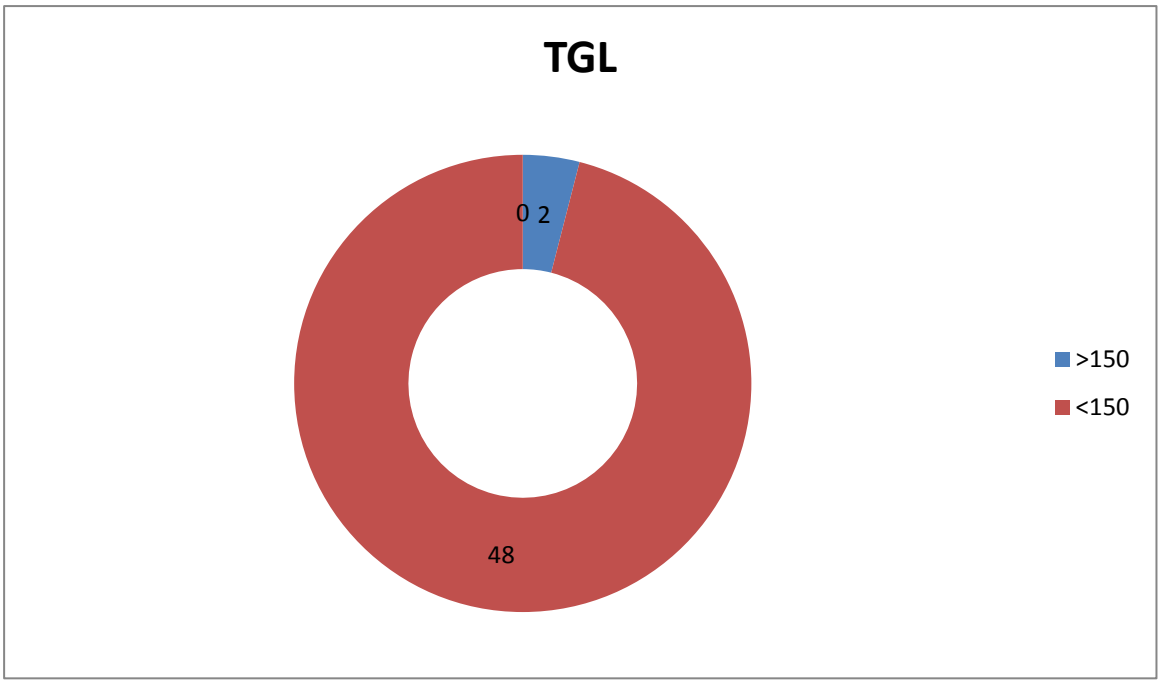
HOMA 2 IR VS AGE

Age in years		HOMA 2		Total
		No Problem	Problem	
30-40	Count	13	3	16
	%within HOMA 2	36.1%	21.4%	32.0%
41-50	Count	10	8	18
	% within HOMA 2	27.8%	57.1%	36.0%
51-60	Count	10	3	13
	% within HOMA 2	27.8%	21.4%	26.0%
Above 60	Count	3	0	3
	% within HOMA 2	8.3%	.0%	6.0%
Total	Count	36	14	50
	% within Age in years	72.0%	28.0%	100.0%
	% within HOMA 2	100.0%	100.0%	100.0%

In this chart, we can see age wise distribution of presence of insulin resistance is shown.

In our study, out of 50 patients, 14 patients have insulin resistance which comes to around 28%. Out of 14 patients , 3 patients(21.4%) were in age group 30-40 years, 8 patients(57.1%) in 41-50 years group, 3 patients (21.4%) in 51- 60 years age group and no one were above 60 years group.

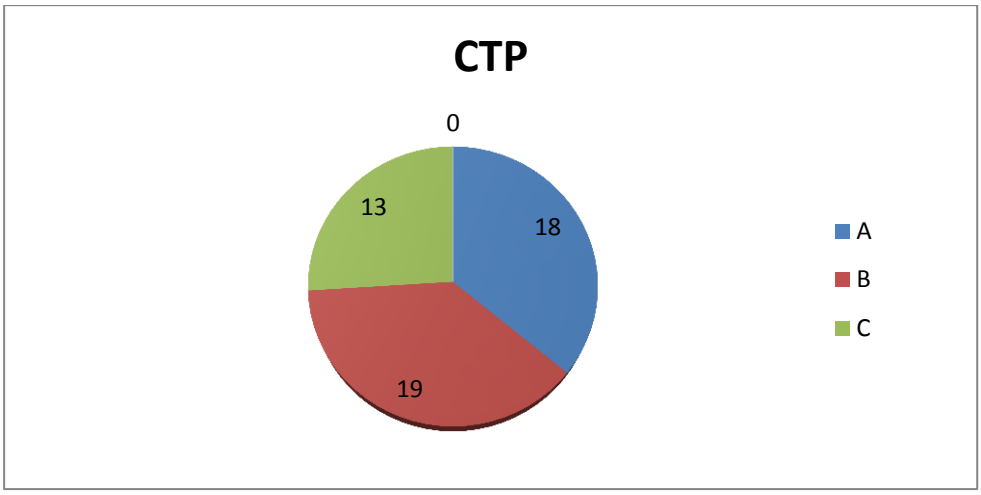
FASTING TRIGLYCERIDES:



This pie chart shows triglyceride levels in our study group

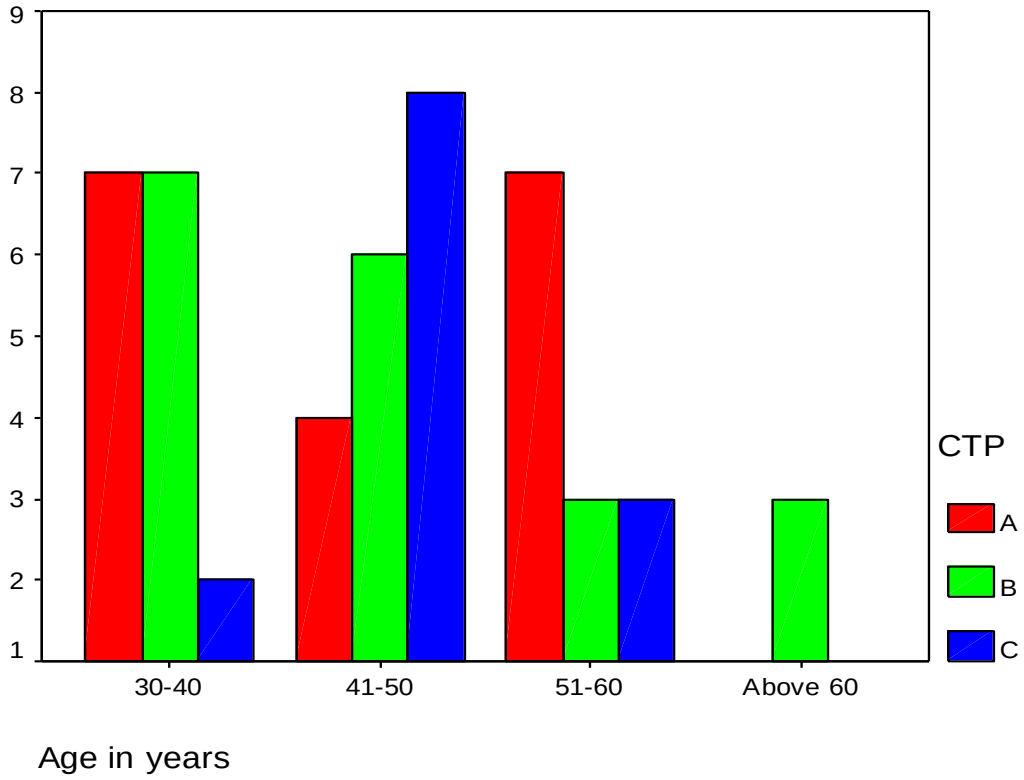
In our study, out of 50 patients only two patients had fasting triglyceride values > 150 mg/dl, with majority had values < 100 mg/dl.

CHILD TURCOTT PUGH SCORE (CTP):



This pie chart depicts patients in numbers in three different child class.

In this study, out of fifty patients taken in to study, 18 were in CTP A, 19 in B and 13 in CTP C score.



Bar diagram showing age wise distribution of patients in CTP score

CTP VS AGE

Age in years		CTP			Total
		A	B	C	
30-40	Count	7	7	2	16
	% within CTP	38.9%	36.8%	15.4%	32.0%
41-50	Count	4	6	8	18
	% within CTP	22.2%	31.6%	61.5%	36.0%
51-60	Count	7	3	3	13
	% within CTP	38.9%	15.8%	23.1%	26.0%
Above 60	Count	0	3	0	3
	% within CTP	.0%	15.8%	.0%	6.0%
Total	Count	18	19	13	50
	% within Age in years	36.0%	38.0%	26.0%	100.0%
	% within CTP	100.0%	100.0%	100.0%	100.0%

This chart shows age wise distribution of all three class of patients

In CTP A , out of 18 patients 7 were in the age group pf 30- 40 years, 4 patients were in 41-50 years age group, 7 patients were in 51- 60 years age group and no

one in > 60 years. In CTP B, out of 19 patients 7 were in 30 -40 years age group, 6 in 41-50 years group, 3 in 51- 60 years and 3 in more than 60 years. In CTP C, out of 13 patients 2 were in 30-40 age group, 8 were in 41- 50 years age group and 3 in 51- 60 years age group.

HOMA AND CTP COORELATION:

HOMA 1R		CTP			Total	P value
		A	B	C		
IR -	Count	17	15	1	33	<0.001**
	% within HOMA 1R	51.5%	45.5%	3.0%	100.0%	
	% within CTP	94.4%	78.9%	7.7%	66.0%	
IR +	Count	1	4	12	17	
	% within HOMA 1R	5.9%	23.5%	70.6%	100.0%	
	% within CTP	5.6%	21.1%	92.3%	34.0%	
Total	Count	18	19	13	50	
	% within HOMA 1R	36.0%	38.0%	26.0%	100.0%	
	% within CTP	100.0%	100.0%	100.0%	100.0%	

This table compares insulin resistance by HOMA1 with CTP score.

By HOMA1- IR, among 18 CTP A patients, 1 had insulin resistance, among 19 CTP B patients, 4 had insulin resistance and among 13 CTP C patients, 12 had insulin resistance. As the CTP grade increases, insulin resistance among the patients increases which was statistically significant (p value <0.001).

HOMA 2-IR AND CTP CORRELATION:

HOMA 2		CTP			Total	P value
		A	B	C		
IR -	Count	17	18	1	36	<0.001
	% within HOMA 2	47.2%	50.0%	2.8%	100.0%	
	% within CTP	94.4%	94.7%	7.7%	72.0%	
IR +	Count	1	1	12	14	
	% within HOMA 2	7.1%	7.1%	85.7%	100.0%	
	% within CTP	5.6%	5.3%	92.3%	28.0%	
Total	Count	18	19	13	50	
	% within HOMA 2	36.0%	38.0%	26.0%	100.0%	
	% within CTP	100.0%	100.0%	100.0%	100.0%	

This table compares insulin resistance by HOMA2 with CTP score.

Out of 18 patients in CTP A score, only 1 had insulin resistance according to HOMA 2-IR and out of 19 patients in CTP B score 1 had insulin resistance and out of 13 patients in CTP C score, 12 had insulin resistance. It was found to be statistically very significant p<0.001.

CORRELATION WITH HOMA 1- 1R:

		Pearson cooefficient	P value
BMI	HOMA1-IR	0.422	0.002
FBS	HOMA1-IR	0.461	0.001
Fasting TGL	HOMA1-IR	-0.144	0.320
Fasting Insulin (Microgm/dl)	HOMA1-IR	0.968	<0.001

This table shows correlation of HOMA1 IR with parameters like BMI, fasting insulin, glucose and triglycerides.

There is a positive correlation between insulin resistance and BMI, fasting blood sugar and fasting insulin by HOMA1 IR. There is no correlation between triglycerides and HOMA 1 I

CORRELATION WITH HOMA 2 IR:

		Pearson coefficient	P value
BMI	HOMA 2	0.422	0.002
FBS	HOMA 2	0.351	0.013
Fasting TGL	HOMA 2	-0.101	0.485
Fasting Insulin (Microgram/dl)	HOMA 2	0.935	<0.001

This table shows correlation of HOMA2 IR with parameters like BMI, fasting insulin, glucose and triglycerides.

There is positive correlation between HOMA2 IR and BMI, fasting glucose and fasting insulin. There is no correlation between fasting triglyceride and insulin resistance by HOMA2 IR score.

TyG index:

All the 50 patients had TyG index < 4.68 in our study.

BASELINE DESCRIPTIVE CHARACTERISTICS OF THE STUDY GROUP:

	N	Minimum	Maximum	Mean	Std. Deviation
Age in years	50	30	75	46.18	9.78
BMI	50	15.79	46.25	22.13	5.09
FBS	50	60	126	100.10	27.77
FBS MMOL/L	50	3.3	9.60	5.56	1.54
Fasting TGL	50	56	172	89.36	26.30
Fasting Insulin (Microgm/dl)	50	3.00	58.09	12.41	11.60
HOMA 1R	50	.50	16.78	3.27	3.50
HOMA 2	50	.4	7.3	1.53	1.28
TyG index	50	3.3	4.0	3.61	.172
Valid N (listwise)	50				

DISCUSSION

DISCUSSION

Diabetes can lead to non alcoholic fatty liver disease and non alcoholic steatohepatitis and ultimately cirrhosis. But conversely cirrhosis can lead to impaired glucose tolerance and diabetes. Diabetes occurring in the setting of cirrhosis is called hepatogenous diabetes. Hepatogenous diabetes has little micro and macrovascular complications [61]. The present study was conducted to know whether cirrhosis is an insulin resistant state or not because in future it may lead to impaired glucose tolerance and frank diabetes.

AGE:

The mean age of our study population is 46.18 years and majority are in the age group of 41- 50 years. According to study conducted by Mukherjee et al from Calcutta National Medical College, the mean age of cirrhotic population was 44 ± 10.2 years[62]. A study conducted by Goswami et al from Jodhpur found the mean age of cirrhotic population was 52.3 ± 13.7 years [63]. There was a cross sectional study conducted in a teaching hospital in Assam by Jyotiprakash et al to find the lipid profile abnormalities in alcoholic cirrhosis showed mean age group of alcoholic cirrhosis was 41- 50 years [64]. According to Doud's et al, the mean age of alcoholic cirrhosis in south Asian male was 44 years[65].

SEX:

According to our study, cirrhosis of liver was common among male population with male female ratio of 15:1. A study by Bhargava et al, the male female ratio was found as 6:1. Another study by Sarkar et al., also showed that 86% of cases of cirrhosis were males and 14% were females. The male preponderence of cirrhosis in South India is due to its etiology alcohol which is more common in males [(66,)]. In Western population the most common cause of cirrhosis is due to HCV because of high prevelance of intravenous drug abuse (14). A study by Sinha et al., found that 99 % of cirrhotics in their study were male. The Dionysos study group found a male: Female ratio of 9:1 in alcoholic cirrhosis[(67)] .

CHILD TURCOTT PUGH SCORE (CTP):

In our study, majority of patients are in CTP B (38%) followed by CTP A(36%).

In our study, we used three scores to assess insulin resistance and then association of insulin resistance with serum triglycerides was assessed. We took the reference values according to Bruno Geloneze et al ,where the cut off value for diagnosing insulin resistance using HOMA1 was >2.7 and using HOMA 2 IR it was > 1.8 [(68)].

HOMA 1-1R:

In our study, insulin resistance by HOMA-1 IR was present in 17 patients out of 50, which constitutes about 34 % which is statistically significant (p value < 0.05). The common age group showing insulin resistance by HOMA1-IR in our study is 41-50 years (36%) followed by 30 - 40 years (32%).

HOMA2 IR:

Insulin resistance was found in 14 patients out of 50 by HOMA 2 contributing to 28% which is statistically highly significant (p value 0.002). The common age group showing insulin resistance by HOMA 2 in our study is 41-50 years (36%) followed by 30-40 years (32%).

There was a study conducted by Goswami. et. Al from Jodhpur, India which showed that insulin resistance was present in 68.5% of euglycemic cirrhotics and universally present in all cirrhotics with recent diabetes.

A study conducted in Spain by Eva Erice et al on insulin resistance in patients with cirrhosis and portal hypertension showed that insulin resistance was present in 60 % of the study population. Insulin resistance in this group was assessed by HOMA 2 index. They concluded that IR prevalence might increase upto 70 % if the patients had concomitant portal hypertension with HVPG > 10mmHg[(69)].

A cross sectional study done in Kolkata by Mukherjee et.al showed the prevalence of impaired glucose tolerance is estimated to about 60- 80 % and overt diabetes in 7- 15%[70] . In that study, about 74 % of cirrhosis was due to alcohol, 14 % was due to hepatitis C virus and 2.9 % was due to autoimmune hepatitis. This study also showed IGT and diabetes were frequently higher in patients aged >45 years. But etiology had not influenced IGT and diabetes according to their study.

A study conducted by Bonora et al showed inverse correlation between clamp mediated glucose disposal and HOMA estimated insulin sensitivity. They also validated the study for use in large epidemiological purposes [71]. A study conducted by Fernando. et al from Mexico showed TyG index and HOMA were almost similar in assessing IR. But in our study, even patients who showed insulin resistance by HOMA 1 and HOMA 2 index, failed to show values above the cut off for TyG index which was taken as 4.6.

As liver is the hub of major lipid synthesis and metabolism, dearrangements in lipid profile can be expected in liver cirrhosis. According to Jyotiprakash et al, study from north eastern India, they concluded that serum total cholesterol values are lowered in alcoholic cirrhotic patients compared with the normal, healthy individuals. The serum HDL cholesterol and LDL cholesterol levels are also significantly decreased compared with the normal controls but serum triglycerides were significantly increased in cases

than controls. Kackar *et al*. found that the serum cholesterol levels decreases progressively with the progress of alcoholic cirrhosis[72].

In a Nigerian study, the median total cholesterol and HDL cholesterol levels were significantly higher in controls compared with cirrhotic patients; however, LDL cholesterol levels were higher in controls compared with cirrhotic patients and the difference was not statistically significant. However, alcoholic cirrhosis may be associated with increased total cholesterol and LDL cholesterol levels, as found by Varghese et al [73].Another Indian study showed elevated triglycerides with decreased serum cholesterol in cirrhosis [74].

In our study, we found that serum triglycerides were not elevated and so TyG index which is calculated based on triglycerides and fasting glucose failed to detect IR in those who are detected by HOMA model.

INSULIN RESISTANCE AND CTP:

Insulin resistance was found mostly in CTP C patients by both HOMA 1IR and HOMA2 IR which contributed to about 92 % and 92.3% of cases with HOMA 1 IR and HOMA 2 IR respectively. This is consistent with study from Jodhpur, India by Goswami & Bargava et al where they showed significant increase in insulin resistance in patients with CTP> 10 and MELD > 15. However, another Indian study by Mukherjee et al from Calcutta showed no correlation with CTP score or with duration of illness

CONCLUSIONS

- The majority of patients with cirrhosis in our study are in the age group of 41- 50 years.
- About 94% of patients included are males.
- Majority of population included are in CTP B followed by CTP C.
- Insulin resistance is found in 34 % of patients using HOMA 1IR and 28% of patients using HOMA 2 IR.
- TyG index failed to show insulin resistance in those shown by HOMA model.
- Serum triglyceride levels are not elevated in our study population.
- Insulin resistance is significantly higher in patients with CTP C by both HOMA 1 and HOMA 2.
- Advancement of liver disease as indicated by CTP C shows increase in insulin resistance and compensatory increase in pancreatic beta cell function as indicated by HOMA 2
- Insulin resistance demonstrated in these euglycemic cirrhotics has no correlation with serum triglyceride levels.
- So, occurrence of impaired glucose tolerance and diabetes is a major concern in these patients which could definitely have bearing upon treatment strategy as they have increased risk of deaths related to

complications of liver cirrhosis like gastrointestinal haemorrhage and hepatocellular carcinoma.

Finally to conclude, cirrhosis of liver is an insulin resistant state and insulin resistance in these euglycemic cirrhotics is not related to serum triglyceride levels.

LIMITATIONS OF THE STUDY

- Very small sample size
- Duration of cirrhosis is not considered.
- Insulin resistance with respect to different etiologies are not considered.
- Relationship with sex and insulin resistance could not be assessed due to small number of female patients included in our study.
- Vitamin D levels were not assessed as decrease in their levels increase insulin resistance in cirrhosis.
- For some patients previous records could not be obtained about glycemic status.
- Further follow up of patients were not done, hence further assessment of glycemic status could not be done.

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ANNEXURES

PROFORMA

NAME:

AGE:

SEX:

ADDRESS:

HISTORY:

h/o Any drug intake in prior two weeks

h/o Any respiratory illness

h/o Alcohol intake

h/o Previous blood transfusion, tattooing, iv drug abuse

h/o TPN

GENERAL EXAMINATION

Height:

Weight:

CVS:

RS:

P/A:

CNS:

INVESTIGATION

1. Blood glucose –fasting
2. Fasting serum triglycerides
3. Fasting insulin levels
4. Blood urea, serum creatinine
5. Liver function test with enzymes
6. Ultrasonogram
7. HBsAg, Anti-HCV

SIGNATURE OF INVESTIGATOR

NAME	AGE	SEX	DECOMPENSATION	WEIGHT(kg)	HEIGHT(m)	BMI	FASTING BLOOD SUGAR mg/dl	FBS MMOL/L	FASTING TGL mg/dl	FASTING INSULIN (microgm/dl)	HOMA IR	HOMA 2	TYG Index	CTP
PATCHAIYAPPAN	43	M	+	70	1.57	27.18	117	6.50	65	58.09	16.78	7.3	3.58	C
KRISHNAVENI	75	F	+	30	1.3	15.98	110	6.11	85	5.44	1.48	0.7	3.67	B
BALARAMAN	44	M	+	55	1.53	22.21	110	6.11	95	23.28	6.32	3.1	3.72	C
PERUMAL	65	M	+	65	1.6	24.22	120	6.67	80	8.33	2.47	1.2	3.68	B
MURUGAN	32	M	+	58	1.62	20.96	97	5.39	75	3	0.72	0.4	3.56	B
JAYENDREN	53	M	+	60	1.6	22.27	112	6.22	70	13.22	3.66	1.8	3.59	B
SUBRAMANI	48	M	+	56	1.57	21.50	67	3.72	70	11.74	1.94	1.4	3.37	B
JAISHANKAR	47	M	+	61	1.61	22.38	76	4.22	80	3.76	0.71	0.5	3.48	B
AUGUSTIN	33	M	-	41	1.5	18.22	75	4.17	75	4	0.74	0.5	3.45	A
SENTHILKUMAR	39	M	+	46	1.64	15.99	65	3.61	115	3.1	0.50	0.4	3.57	A
MURUGAN	36	m	+	46	1.64	15.99	60	3.33	65	3.5	0.52	0.4	3.29	A
BASKAR	40	M	+	50	1.6	18.36	97	5.39	70	15.59	3.73	2	3.53	A
KARNAN	33	M	+	50	1.54	19.82	96	5.33	114	4.77	1.13	0.6	3.74	B
SHAKTHI KUMAR	32	M	+	45	1.62	16.00	90	5.00	170	9.56	2.12	1.2	3.88	B
RAVI	39	M	-	60	1.66	21.77	71	3.94	56	8.48	1.49	1	3.30	B
MARIMUTHU	52	M	+	53	1.64	18.59	82	4.56	61	5.1	1.03	0.6	3.40	B
SARIF JOHN	54	M	+	70	1.56	27.53	123	6.83	143	7.01	2.13	1	3.94	C
SWAMINATHAN	55	M	+	65	1.65	22.77	62	3.44	100	22.15	3.39	2.5	3.49	C
NABI	42	M	+	51	1.58	19.23	126	7.00	75	4.5	1.40	0.6	3.67	B
CHANDRAN	54	M	+	80	1.66	27.94	78	4.33	82	4.5	0.87	0.6	3.50	A
MUTHULAKSHMI	46	F	-	46	1.5	20.44	118	6.56	81	6.36	1.85	0.9	3.68	A
GOVINDARAJ	49	M	+	117	1.57	46.25	123	6.83	120	25.1	7.62	3.4	3.87	C
ARUMUGAM	60	M	+	56	1.46	24.86	101	5.61	98	6.8	1.70	0.9	3.69	A
KARUNANIDHI	49	M	+	66	1.56	25.89	115	6.39	99	7.2	2.04	1	3.76	B
SEKAR	43	M	+	49	1.47	21.29	120	6.67	56	25.04	7.42	3.5	3.53	C
RAMKUMAR	42	M	+	70	1.57	27.18	116	6.44	65	56	16.04	3.5	3.58	C
KARTHIK	44	M	+	56	1.54	22.35	110	6.11	96	23.5	6.38	3.1	3.72	C
PALANIYAMMAL	60	F	-	48	1.56	19.70	86	4.78	90	6	1.27	0.8	3.59	A
PERUMAL	64	M	+	65	1.6	24.22	117	6.50	82	12	3.47	1.8	3.68	B
SATHISH	33	M	+	59	1.62	21.34	100	5.56	78	3	0.74	0.4	3.59	A
JAYAKUMAR	54	M	+	62	1.62	22.48	118	6.56	76	15	4.37	2	3.65	B
VIJAYAKUMAR	48	M	-	58	1.59	22.94	68	3.78	72	13	2.18	1.5	3.39	A
AHAMED	47	M	+	62	1.63	22.21	78	4.33	82	4.5	0.87	0.6	3.50	A
KISHORE	34	M	+	42	1.56	16.03	75	4.17	78	4.8	0.89	0.6	3.47	A
KUMAR	39	M	+	46	1.65	15.79	68	3.78	115	8.1	1.36	1	3.59	B
RAJA	36	M	+	46	1.64	15.99	60	3.33	68	3.9	0.58	0.5	3.31	A
BASKAR	40	M	+	51	1.57	19.47	98	5.44	72	16	3.87	2.1	3.55	C
AROKIASAMY	31	M	+	50	1.54	19.82	98	5.44	116	5.6	1.36	0.7	3.75	B
ASHOK	45	M	-	60	1.66	21.77	94	5.22	172	10	2.32	1.3	3.91	B
SUBRAMANI	40	M	+	60	1.66	20.69	72	4.00	66	11	1.96	1.3	3.38	B
ANAND	52	M	+	53	1.64	18.59	82	4.56	65	7.3	1.48	0.9	3.43	A
DINESH	54	M	+	70	1.57	27.18	125	6.94	145	8.4	2.59	1.1	3.96	A
KASINATHAN	42	M	-	52	1.58	20.83	126	7.00	76	20	6.22	2.7	3.68	C
JAMES	55	M	+	65	1.65	22.77	64	3.56	100	24	3.79	2.7	3.51	C
SIVA	54	M	+	72	1.68	24.45	78	4.33	88	9.1	1.75	1.1	3.54	A
ESWARI	47	F	+	49	1.51	20.17	124	6.89	82	8	2.45	1.1	3.71	A
DIVAKAR	49	M	+	96	1.68	32.95	125	6.94	110	26	8.02	3.5	3.84	C
MUNUSAMY	56	M	-	56	1.5	24.88	102	5.67	98	3.5	0.88	0.5	3.70	A
KATHIRESAN	49	M	+	66	1.56	25.89	116	6.44	98	8.4	2.41	1.2	3.75	B
VEERASAMY	32	M	+	56	1.65	19.47	119	6.61	78	24	7.05	3.4	3.67	C

நோயாளி ஒப்புதல் படிவம்

ஆராய்ச்சியின் விவரம்:

ஆராய்ச்சி மையம்: அரசு ராயப்பேட்டை மருத்துவமனை

நோயாளியின் பெயர்: நோயாளியின் வயது:

பதிவு எண்:

1. மேற்குறிப்பிட்டுள்ள ஆராய்ச்சியின் நோக்கத்தையும் பயனையும் முழுவதுமாக புரிந்துகொண்டேன். மேலும் எனது அனைத்து சந்தேகங்களையும் கேட்டு அதற்கான விளக்கங்களையும் தெளிவுபடுத்திக் கொண்டேன்.
2. மேலும் இந்த ஆராய்ச்சிக்கு எனது சொந்த விருப்பத்தின் பேரில் பங்கேற்கிறேன் என்றும், மேலும் எந்த நேரத்திலும் எவ்வித முன்னறிவிப்புமின்றி இந்த ஆராய்ச்சியிலிருந்து விலக முழுமையான உரிமை உள்ளதையும், இதற்கு எவ்வித சட்ட பிணைப்பும் இல்லை என்பதையும் அறிவேன்.
3. ஆராய்ச்சியாளரோ, ஆராய்ச்சி உதவியாளரோ, ஆராய்ச்சி உபயத்தாரோ, ஆராய்ச்சி பேராசிரியரோ, ஒழுங்குநெறி செயற்குழு உறுப்பினர்களோ எப்போது வேண்டுமானாலும் எனது அனுமதியின்றி எனது உள்நோயாளி பதிவுகளை இந்த ஆராய்ச்சிக்காகவோ அல்லது எதிர்கால பிற ஆராய்ச்சிகளுக்காகவோ பயன்படுத்திக்கொள்ளலாம் என்றும் மேலும் இந்த நிபந்தனை நான் இவ்வராய்ச்சியிலிருந்து விலகினாலும் தகும் என்றும் ஒப்புக்கொள்கிறேன். ஆயினும் எனது அடையாளம் சம்பந்தப்பட்ட எந்த பதிவுகளும் (சட்டபூர்வமான தேவைகள் தவிர) வெளியிடப்படமாட்டது என்ற உறுதிமொழியின் பெயரில் இந்த ஆராய்ச்சியிலிருந்து கிடைக்கப்பெறும் முடிவுகளை வெளியிட மறுப்பு தெறிவிக்கமாட்டேன் என்று உறுதியளிக்கின்றேன்.

4. இந்த ஆராய்ச்சிக்கு நான் முழுமனதுடன் சம்மதிக்கின்றேன் என்றும் மேலும் ஆராய்ச்சிக் குழுவினர் எனக்கு அளிக்கும் அறிவுரைகளை தவறாது பின்பற்றுவேன் என்றும் உறுதியளிக்கின்றேன்.
5. இந்த ஆராய்ச்சிக்குத் தேவைப்படும் அனைத்து மருத்துவப் பரிசோதனைகளுக்கும் ஒத்துழைப்பு தருவேன் என்று உறுதியளிக்கின்றேன்.
6. இந்த ஆராய்ச்சிக்கு யாருடைய வற்புறுத்தலுமின்றி எனது சொந்த விருப்பத்தின் பேரிலும் சுயஅறிவுடனும் முழுமனதுடனும் சம்மத்திக்கின்றேன் என்று இதன் □ லம் ஒப்புக்கொள்கிறேன்.

நோயாளியின் கையொப்பம் / பெருவிரல் கைரேகை

இடம்: தேதி:

ஆராய்ச்சியாளரின் கையொப்பம்

இடம்: தேதி:

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.3182/ME-1/Ethics/2014 Dt:08.05.2014.
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on to establish that cirrhosis of liver is an insulin resistant state and to correlate whether insulin resistance is due to elevated triglyceride level in euglycemic cirrhotics- For Project work submitted by Dr.Kiruthika.S, MD (GM), PG Student, KMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
30 MAY 2014
Kilpauk, Chennai-10.

30/5/14.

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai